THE ROLE OF SOMATOSENSORY AFFERENCES IN PARKINSON'S DISEASE

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DECLARATION THAT THE WORK PRESENTED IN THIS THESIS IS THE CANDIDATE'S OWN

I, Antonella Macerollo, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

London, 13th April 2018

Signature

To my most precious diamond, Silvia

To my love, Gianluca

To my infinitely lovable parents, Dony & Nicola

ABSTRACT

Parkinson's disease (PD) is the second most common neurodegenerative disorder in the world. The primary motor symptom of PD is bradykinesia, a slowing and reduction in amplitude of voluntary movement.

Here, I aim to test some neurophysiological aspects of PD. Furthermore, I explored the possibility to develop non-invasive treatment for this group of patients.

The first two studies tested the contribution of a specific phenomenon labelled sensory attenuation or sensory gating in the motor symptoms of PD, especially bradykinesia. I found that the sensory attenuation is abnormal in this group of patients. Especially, PD patients OFF medications showed a reduced sensory attenuation measured as the amplitude of the somatosensory evoked potentials. Interestingly, I found that the sensory attenuation was equal to the healthy age matched controls when the patients were tested in ON pharmacological state.

Additionally, this research tested a theory of the functional role of sensorimotor beta oscillations that could explain beta power modulations in healthy subjects and the increase in beta power observed in PD patients. My results were in line with the previous data presented in the literature. Indeed, I found the increase beta power in both my two cohorts of PD patients. Finally, I tested a potential correlation between the abnormalities of these two phenomena in PD: reduced sensory attenuation and increased beta oscillations. I did not find any significant correlation between the two phenomena. They might be two different neurophysiological mechanisms

underlying this disease. However, further studies are necessary to investigate this hypothesis.

Having tested the influence of the somatosensory signal in some motor symptoms, the second part of the thesis was focused on the development of non-invasive treatments of bradykinesia in PD. I tested the impact of vibratory stimuli to improve these motor signs. In particular, several frequencies of vibration have been tested through different devices applied to the wrist. The device was called “Emma watch” and I found that the application of vibration with the modulation of 60 bpm improved the bradykinesia in PD patients

Finally, I presented a case study regarding the benefit of vibratory stimulation on the freezing of gait thought shoe insoles generating vibration. The tested patient showed an improvement of the frequency of the freezing episodes after a week wearing the insoles, which generated vibration at 200 Hz.

IMPACT STATEMENT

This thesis brings innovative knowledge and discoveries in the field of Neurology and Neuroscience, which are beneficial in the academia as well as outside it. Indeed, the neurophysiology results on the pathophysiology of PD open the scenario to develop further studies to investigate the correlation between SA and beta oscillations. These two phenomena might become the target of further treatments to improve this neurodegenerative disease. Consequentially, these studies will bring further collaborations with the field of pharmacology as well as functional therapy, as DBS.

Yes, the devices generating vibration tested here to improve bradykinesia will bring the team to develop stronger collaborations with other research areas as biomechanics, biomedical engineering to finalize the device with the most useful characteristics in terms of frequency and amplitude of the vibration. Furthermore, collaboration with informatic engineering is mandatory in the further study to improve the software to programme the device. This might lead to develop an app to allow patients to change the parameters of vibration at home to reach the best control of their symptoms.

Developing further studies on the base of the current results will requires to develop grants applications to have funding for the next scholarships. The latter are an academic benefit for our team but also for the local academic community.

The data presented in this thesis will be spread out in medical journals. Consequentially, the academic benefits will have an impact not only locally but also at the national and international level.

All these benefits inside the academia are strictly connected to the potential benefits outside the academia. Indeed, the encouraging results regarding the improvement of PD signs with vibratory devices will lead to produce devices that might be used in the clinical practice to help this group of patients. This is particularly important for the freezing of gait that is a neurological sign resistant to the current pharmacotherapies as well as surgical interventions. Thus, it is mandatory to explore innovative tools to try and improve this deficit.

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LIST OF ABBREVIATIONS

AbPB = Abductor Pollicis Brevis

ABC = Activities-Specific Balance Confidence

ANOVA = Analysis of Variance

BG = Basal Ganglia

DBS = Deep Brain Stimulation

DCM = Dynamic Causal Modelling

DC-ML = Dorsal-Column Medial Lemniscus

dSPNs = direct pathway SPNs

ECoG = Electrocorticogram

EEG = Electroencephalogram

EMG = Electromyography

ERD = Event-Related Desynchronization

ERS = Event-Related Synchronization

EPSPs = Excitatory Postsynaptic Potentials

FFABQ = Fear of Falling Avoidance-Behavior Questionnaire

FOG = Freezing of Gait

GABS = Gait and Balance Scale

GBA = glucocerebrosidase gene

GFQ = Gait and Falls Questionnaire

GPe = external Globus Pallidus

GPi = internal Globus Pallidus

HD = Huntington’s Disease

HS = Hamstring Muscles

IPSPs = Inhibitory Postsynaptic Potentials

iSPNs = indirect pathway SPNs

LFPs = Local Field Potentials

MEG = Magnetoencephalography

MEPs = Motor-Evoked Potentials

MN = Median Nerve

PD = Parkinson’s Disease

PMBS = Post-movement Beta Synchronization

PMC = Pre-Motor Cortex

PN = Peripheral Nerve

PPN = Pedunculo-Pontine Nucleus

Q = Quadriceps

ROI = Region of interest

SA = Sensory Attenuation

SC = Spinal Cord

SMA = Supplementary Motor Area

SNpc = Substantia Nigra pars-compacta

SPNs = Spiny Projection Neurons

SSEPs = Somato-Sensory Evoked Potentials

STN = Subthalamic Nucleus

TMS = Transcranial Magnetic Stimulation

tACS = Transcranial Alternating Current Stimulation

TA = Tibialis Anterior

TS = Triceps Surae

TVR = Tonic Vibration Reflex

UPDRS = Unified Parkinson's Disease Rating Scale

VIM = Ventralis Inter-Medius nucleus

Chapter 1. INTRODUCTION

1.1 Parkinson's disease

1.1.1 Clinical features of Parkinson's disease

This PhD is focused on the investigations of neurophysiological aspects of Parkinson's disease (PD).

PD commonly presents in the clinical practice with impairment of dexterity or, less commonly, with a slight dragging of one foot. The onset is commonly unilateral and gradual. Indeed, PD patients usually attend the movement disorders clinic many years after the onset of the first symptoms, which might be unnoticed or misinterpreted for a long time (Cheron, Dan, & Borenstein, 2000; Lees, Hardy, & Revesz, 2009). Family members or work colleagues might notice some changes in the face expression and/or abnormalities in the speech. These changes are rarely noticed by the patient apart from early loss of smell, which is occasionally spontaneously reported by the patient (Doty, Bromley, & Stern, 1995).

The three cardinal motor symptoms of PD are *bradykinesia* (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions), *cogwheel rigidity* (the muscular rigidity in which passive movement of the limbs elicits ratchet-like start-and stop movements through the range of motion of a joint, i.e. the elbow), *rest tremor* (a type of tremor occurring in a body part that is relaxed and completely supported against gravity). Postural and gait impairment complete the clinical picture, especially in the late stage of the disease (Kalia & Lang, 2015).

In summary, bradykinesia is defined as slowness of initiation of voluntary movement with progressive reduction in speed and amplitude or repetitive actions. A slow progression, unilateral presentation with asymmetrical signs, a pill rolling rest tremor, cogwheel rigidity and good sustained response to L-dopa support the diagnosis (Goetz et al., 2008).

Episodes of *freezing of gait* (FOG) represent the typical gait impairment in PD patients. The FOG is defined as “a brief episode during which patients find it impossible to generate effective forward stepping movements, in the absence of a cause other than parkinsonism or higher cortical deficits. It is most commonly experienced during turning and step initiation, but also when faced with a special constraint such as a doorway, stress and distraction. Focused attention and external stimuli (cues) can overcome the episode. Because of its sudden and unpredictable nature, FOG often leads to falls and injuries” (Giladi & Nieuwboer, 2008). There are three different phenotypes of FOG: shuffling with small steps, trembling in place without forward movement, or total akinesia (Schaafsma et al., 2003).

The clinical practice suggests two major subtypes of PD: tremor-dominant PD and non-tremor-dominant PD (which includes phenotypes described as akinetic-rigid syndrome and postural instability gait disorder) (Marras & Lang, 2013). Motor signs related to long-term symptomatic treatment including motor fluctuations and dyskinesia complete the motor picture in the advanced stages (Hely, Morris, Reid, & Trafficante, 2005). Notably, it is currently well known that PD is not a pure motor disorder but includes several other non-motor features, including olfactory dysfunction, cognitive impairment, psychiatric symptoms, sleep disorders (excessive daytime

sleepiness, and rapid eye movement sleep behaviour disorder), constipation, autonomic dysfunction, dysphagia, pain, and fatigue (Sauerbier, Jenner, Todorova, & Chaudhuri, 2016).

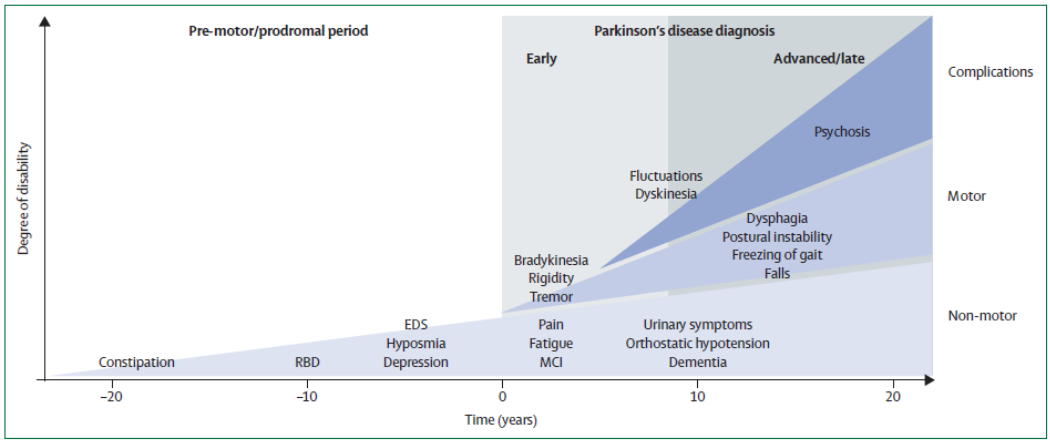


Figure 1.1.1.1. *Clinical symptoms and time course of Parkinson's disease progression (Kalia & Lang, 2015).*

Diagnosis of PD occurs with the onset of motor symptoms (time 0 years) but can be preceded by a premotor or prodromal phase of 20 years or more. This prodromal phase is characterised by non-motor symptoms. Axial motor symptoms, such as postural instability with frequent falls and freezing of gait, tend to occur in advanced disease. Long-term complications of dopaminergic therapy, including fluctuations, dyskinesia, and psychosis, also contribute to disability.

EDS=excessive daytime sleepiness.
MCI=mild cognitive impairment.
RBD=REM sleep behaviour disorder.

1.1.2 General pathophysiology of Parkinson's disease

Though the major anatomical site of neurodegeneration – the basal ganglia - and the main neurotransmitter involved – dopamine – have been known for many years, it has been surprisingly difficult to provide a clear neurobiological mechanism for the fundamental movement deficit in PD, which is the bradykinesia.

The neurodegeneration of PD is characterized by the presence of severe substantia nigra pars-compacta (SNpc) cells loss (Lees et al., 2009). The most profoundly affected area of the SNpc is typically the ventrolateral tier, which contains neurons that project to the dorsal putamen of the striatum. Moderate to severe dopaminergic neuronal loss within this area is probably the cause of the motor symptoms in PD, bradykinesia and rigidity in particular (Kordower et al., 2013). The neuronal loss in PD involve other brain regions, including the locus coeruleus, nucleus basalis of Meynert, pedunculopontine nucleus, raphe nucleus, dorsal motor nucleus of the vagus, amygdala, and hypothalamus (Dickson, 2012). Notably, the hallmark of PD is Lewy pathology, consisting in accumulation of aggregated α-synuclein in specific brain stem, spinal cord, and cortical regions (Polymeropoulos et al., 1997).

α-synuclein (α-Syn), a neuronal protein encoded by SNCA (synuclein, alpha, non A4 component of amyloid precursor) gene (Nussbaum & Polymeropoulos, 1997) is one of the key proteins implicated in the pathogenesis of PD and the main component of Lewy bodies, the cytoplasmic inclusions which are the histopathological hallmark of PD

(Dehay & Fernagut, 2016). Furthermore, it has been proposed that α-Syn might also accumulate extracellularly (George & Brundin, 2015).

α-Syn plays a key role in propagating the progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNc) (Spillantini et al., 1997). This protein is involved in the characterization of hereditary patterns (PARK 1 locus) (Polymeropoulos et al., 1997) as well as in sporadic forms of PD, and appears to have a multi-system occurrence ranging from the central nervous system to the gastrointestinal tract (Aldecoa et al., 2015; Braak et al., 2006). Of note, recent studies suggested that the gastrointestinal tract may be the starting point of PD onset as shown by the presence of α-Syn in nerve fibers of the colonic submucosa in PD patients at an early stage of the disease (Shannon et al., 2012), and even before the actual onset of motor symptoms. As such, the abnormal aggregation of α-Syn in the gastrointestinal tract might constitute a biomarker of premotor PD, although this finding remains controversial (Gray, Munoz, Gray, Schlossmacher, & Woulfe, 2014; Shannon et al., 2012).

Several studies have investigated the different post-translational alterations of α-Syn as oligomerization, aggregation, and, consequentially, deposition as monomeric, oligomeric and fibrillary aggregation complexes. In line with these findings, a variety of potential pathological modifications have been proposed (Dettmer et al., 2015). Among the post-translational modifications, the phosphorylation of α-Syn, mainly on Ser87 and Ser 129 residues, is the most explored. Indeed, it seems to be a major determinant of neuropathology for patients with PD mediated through the potential toxicity of the deposits of this molecule (Anderson et al., 2006).

The development of ‘post-translational’ treatment strategies addressing a more fundamental pathophysiological process such as the toxicity of α-Syn misfolding represents an intriguing and important strategy to counteract the pathological deposition of α-Syn and by default address both motor and non-motor aspects of PD symptom expression.

Genome-wide association studies in PD have demonstrated a number of significant genetic associations. However, the most exciting of all genetic associations with PD is the identification that the homozygotes (Gaucher’s disease patients) as well as heterozygote mutations carriers of the glucocerebrosidase gene (GBA1) have a significant risk factor for the disease as well as a higher rate of clinical progression (Beavan & Schapira, 2013; Schapira, 2015; Winder-Rhodes et al., 2013). The most challenging aspect of this finding has been the discovery of a strong relationship between GBA and α-Syn pathology (Schapira, 2015). The presence of a GBA1 mutation is invariably associated with a reduction in GCBA enzyme activity. Interestingly, the reduced activity of GBA lead to an overexpression of α-Syn misfolded toxic aggregates (Shapira, 2015). Conversely, overexpression of α-Syn cause a reduction in GBA activity and the two factors are involved in a closed loop (Shapira, 2015).

In recent years, immunological mechanisms have been thoroughly investigated as potential targets to modulate neurodegeneration in several conditions. It is well known that immunization against a specific disease can be reached through two different mechanisms: active as well as passive immunization. These mechanisms are different but may be complementary in some circumstances. The active immunization is the induction of

immunity after exposure to an antigen as it is reached by vaccines. Indeed, they consist in the administration of antigenic material to stimulate an individual's immune system to develop adaptive immunity to a specific pathogen. On the contrary, the passive immunity involves the transfer of active humoral immunity in the form of ready-made antibodies directed against a specific pathogen or toxin. Methods of active immunization through vaccination approach has increasingly been investigated as a potential treatment for different synucleinopathies, including not only PD but also multiple system atrophy and dementia with Lewy bodies (Schneeberger, Tierney, & Mandler, 2016).

Substantial advances in the understanding of the pathogenesis of PD have resulted from the epidemiological findings, pathological observations, and genetic discoveries over the last twenty years. It seems that abnormalities in the regulation of protein homoeostasis are implicated in the pathogenesis of PD. Especially abnormalities in protein aggregation, intracellular protein and membrane trafficking, and protein disposal by the ubiquitin-proteasome and lysosome-autophagy systems. New discoveries in genetics of PD has also suggested a role for aberrations in synaptic structure and function in the pathogenic process and has showed the importance of mitochondrial dysfunction (Bezard & Przedborski, 2011). Additionally, a potential role of neuroinflammation in the promotion or in the protection of neurodegeneration is currently under debate. Interestingly, a single-nucleotide polymorphism within the human leucocyte antigen region has been associated with a risk of developing PD, suggesting an immune-related genetic susceptibility to this neurodegenerative disease (Nalls et al., 2014). A reduced risk of PD has recently been associated with the use of

anti-inflammatory medications supporting the hypothesis that inflammation might promote an underlying disease process (Noyce et al., 2012).

1.1.3 Sensorimotor beta oscillations and Parkinson's disease

During the PhD, the abnormalities of sensorimotor beta oscillations in PD were one of pathophysiological aspects that I was interested to study.

Neurons, especially in thalamic nuclei and in the cerebral cortex, exhibit intrinsic oscillations, which probably form the basis for macroscopic rhythms, detectable with electroencephalography (EEG) and magnetoencephalography (MEG).

In the motor cortex, oscillatory activity has been reported at a variety of frequencies between: 4 and 60 Hz. Oscillatory beta activity is in the frequency range between 15 Hz and 30 Hz and they have their origin in several brain areas (Engel & Fries, 2010). I was interested during my PhD to investigate the beta oscillations observed specifically in the sensorimotor cortices in healthy human subjects (Pfurtscheller, Stancak, & Neuper, 1996). It is well established that beta power is modulated by action execution. Beta power decreases when we move and is transiently increased once the movement has stopped (post-movement beta synchronization, PMBS) (Pfurtscheller & Lopes da Silva, 1999). However, despite extensive research into these neuronal oscillations their functional role, if any, remains unknown. Several hypotheses have been postulated regarding the functional role of beta oscillations.

Beta cortical oscillations can be split into two sections: beta 1 (13-20 Hz; predominantly subcortical networks) and beta 2 (20–35 Hz; predominantly cortical networks) (Rangaswamy et al., 2002).

In considering the functional importance of beta cortical oscillations, it was tempting to attempt parallels with the visual system, where experimental and theoretical evidence is accumulating in favour of the idea that they act to subserve binding of the disparate features of the visual scene into a unified percept (S. N. Baker, Kilner, Pinches, & Lemon, 1999). As in the visual system, the motor system is characterised by a number of different cortical areas, which are to some extent specialised for different functions. It is possible that synchronous oscillations are used, as in the visual cortex (Engel, Konig, Kreiter, & Singer, 1991), to permit reliable communication between different motor areas (Donoghue, Sanes, Hatsopoulos, & Gaal, 1998). However, the motor cortex also has an important analytic role. Indeed, it must convert a unified, goal-directed motor plan into the temporal activity of the many muscles which must carry it out. Notably, synchrony, and synchronous oscillations are not a single phenomenon performing one function (S. N. Baker et al., 1999). Importantly 15–30 Hz cortical oscillations may not be caused by a single generator. Pfurtscheller (Pfurtscheller, Stancak, & Edlinger, 1997) provided evidence that one component of the 20 Hz EEG recorded over sensorimotor cortex was motor in origin, whilst another was a harmonic of 10 Hz rhythms, thought to originate from somatosensory cortex (Salenius, Schnitzler, Salmelin, Jousmaki, & Hari, 1997; Salmelin & Hari, 1994). The existence of two distinct types of 20 Hz rhythm in sensorimotor cortex could explain the apparent contradiction between different studies. On the one hand, Baker et al. (S. N. Baker et al., 1999) showed that 20 to 30 Hz oscillations appear most strongly during the hold phase of the precision grip task and disappear during movements. This agrees with other studies showing beta cortical oscillations just before

movement as an “event-related desynchronization” of the EEG and MEG in this frequency range (Manganotti et al., 1998; Pfurtscheller et al., 1996; Salenius et al., 1997). Donoghue et al. (Donoghue et al., 1998) similarly showed oscillations predominantly confined to the period before a movement was produced. Pfurtscheller et al. (Pfurtscheller et al., 1996) demonstrated a post movement synchronisation of EEG following movements, which they interpreted as a sign of “idling” in the motor cortex. By contrast, Murthy and Fetz (Murthy & Fetz, 1992, 1996) reported that oscillations occurred when the monkey performed fine manipulative movements with the hand in the absence of visual feedback. Oscillations in somatosensory cortex have been proposed to play a role in texture discrimination by acting as a “phase locked loop” (Ahissar, 1998); the rhythms seen in motor cortex during fine manipulative movements (Murthy & Fetz, 1992, 1996) could be similar to these and perhaps permit efficient communication between somatosensory and motor cortices.

Engel et al. proposed that beta activity represents the status quo (Engel & Fries, 2010). In other words, beta-band activity seems related to the maintenance of the current sensorimotor or cognitive state. These authors hypothesized that beta oscillations and/or coupling in the beta-band are expressed more strongly if the maintenance of this status quo is intended or predicted, than if a change is expected. Indeed, recent studies support the hypothesis that beta band activity, rather than reflecting a mere lack of movement, may be a signature of an active process that promotes the existing motor set (the status quo) whilst compromising neuronal processing of new movements. For instance, Gilbertson et al. (Gilbertson et al., 2005) demonstrated that spontaneous enhancements of beta band activity are

associated with impairment in movement performance. These results showed that voluntary movements triggered during periods of spontaneous enhanced beta band activity are slowed.

Androulidakis et al. (Androulidakis, Doyle, Gilbertson, & Brown, 2006) showed that corrective responses during a visually controlled postural task are more effective during periods of beta activity, suggesting that the effect of beta synchrony in motor cortex may be the maintenance of steady-state force output. Importantly, Pogosyan et al. (Pogosyan, Gaynor, Eusebio, & Brown, 2009) tried to manipulate the beta band power using transcranial alternating-current stimulation. They entrained the oscillations in the motor cortex to a 20 Hz rhythm whilst subjects performed a visuomotor tracking task. Interestingly, the reaction times were not affected. However, the subject's voluntary movements were decreased in velocity. Koelewijn et al. (Koelewijn, van Schie, Bekkering, Oostenveld, & Jensen, 2008) found enhanced beta band activity rebound following motor errors, as a marker of increased response inhibition.

These studies suggest that the beta band activity may be responsible for the tendency of the sensorimotor system to maintain the status quo. Beta oscillations may allow the more efficient processing of feedback as proprioceptive signals that is required for monitoring the status quo and recalibrating the sensorimotor system (S. N. Baker, 2007). Indeed, it has been showed that beta band activity can modulate processing of stimuli in somatosensory cortex (Lalo et al., 2007).

Other hypotheses for the role of cortical macroscopic oscillations include epiphenomena, with no functional significance, and idling, which would

allow the system to start more rapidly than by cold start (Hari & Salmelin, 1997). Previous data suggested that cortical rhythms might have a role in the co-ordination of neural activity between the central and peripheral nervous systems. Interestingly, Baker and Kilner clarified in different studies that this is not a simple epiphenomenon but it is related to specific motor parameters. Their studies showed significant levels of coherence between cortical oscillatory activities and muscle activities in the 15–30 Hz range. Notably, this coherence presented a specific task-dependent modulation (S. N. Baker et al., 1999; S. N. Baker, Olivier, & Lemon, 1997; Kilner, Baker, Salenius, Hari, & Lemon, 2000). Since activity in this range were functionally and causally related to motor behaviour in itself, this would suggest that motor information is carried by neural synchronization.

In line with these studies are the results of Feurra and collaborators (Feurra et al., 2011). These authors studied the role of beta oscillations with a manipulative approach using a combination of simultaneous single-pulse transcranial magnetic stimulation (TMS) and transcranial alternating current stimulation (tACS) applied at different frequencies. TMS activates trans-synaptically fast-conducting pyramidal corticospinal axons and therefore mimics the physiology of the motor pathways. tACS is a technique used to entrain regional brain oscillations in selected frequencies. Ferrua and collaborators tested 20 Hz frequency (beta range) and some control frequencies (5, 10, and 40 Hz). Interestingly, they showed that all tested frequencies had an enhancing effect on motor-evoked potentials (MEPs). However, only the target frequency of 20 Hz had a statistically significant enhancement compared with control conditions (Feurra et al., 2011).

Moreover, tACS applied on a control site (parietal cortex) and on a peripheral site (ulnar nerve) also failed to modulate MEPs. These results suggest the functional significance of the 20 Hz idling beta rhythm of sensorimotor regions.

The importance of understanding the functional role of beta oscillations is highlighted by the observation that PD patients have a pathologically higher power of beta oscillations sub-cortically in the subthalamic nucleus (Jenkinson & Brown, 2011). The enhanced beta activity in PD patients is consistent with the hypothesis that the beta oscillations is preventing change from the status quo and that this results in the bradykinetic symptoms (P. Brown, 2006). Furthermore, a pathologically increase in cortical beta power has been found in the most advances case of PD (Berendse & Stam, 2007) and confirmed by studies on animals with dopamine depletion (Mallet, Pogosyan, Sharott, et al., 2008). Of note, Pollok showed that beta band oscillations of bilateral primary sensori-motor cortices are already increased at the earliest stages of PD (Pollok et al., 2012).

How does our dorsal striatum and other basal ganglia build the control of movements? What are the neural correlates and mechanisms at the base of motor pathways? On the other hand, what are the neural populations involved in the development of parkinsonian symptoms? These old, yet timely, questions are also the most challenging to investigate. Indeed, identifying the neural correlates of bradykinesia and rigidity requires us to disentangle the dopaminergic pathways in the context of basal ganglia (BG) circuits. The well-known role of dopamine in the ‘direct/indirect pathways’

model of BG organization (DeLong, 1990; Y. Smith, Bevan, Shink, & Bolam, 1998) lead support to the hypothesis that dopamine depletion in idiopathic PD changes the activity of spiny projection neurons (SPNs) in striatum and results in a gross imbalance in the firing rates of direct pathway SPNs (dSPNs) and indirect pathway SPNs (iSPNs). This imbalance is predicted to be the main mechanisms underlying the bradykinesia and rigidity in this group of patients. However, this pathological imbalance in the 'direct/indirect pathways' is not the only involved mechanism. Indeed, several neurophysiological studies have highlighted the complementary role of pathological neural oscillations. Especially, high activity at beta frequencies (15-30 Hz) have been observed in the activity of neurons in external globus pallidus (GPe), subthalamic nucleus (STN), and other BG nuclei outside of striatum. What the link is between these two mechanisms and how the potential complementary role acts in the pathogenesis of bradykinesia/rigidity is still under investigation.

It has recently found that the firing of individual striatal neurons in dopamine-intact control rats as well as in dopamine depleted rats was phase-locked to the cortical slow oscillation (Sharott, Vinciati, Nakamura, & Magill, 2017). In addition, the dopamine depletion state was associated with increases in the firing rates of a subgroup of striatal neurons and an increase in the low-frequency oscillatory power. The latter showed the synchronized output of neuronal ensembles. The recording of individual iSPNs and dSPNs in both dopaminergic states showed that the two populations of neurons have a different neurophysiological pattern only in the dopamine depletion state. Indeed, the increased firing rates were present in both iSPNs and dSPNs but the upper range of firing rates as well as the spontaneously-firing were

larger for iSPNs. Consequently, Sharott et al. supported the hypothesis that iSPNs are the responsible generators of the high overall firing rate and level of low-frequency oscillatory observed in the dopamine-depleted striatal network during cortical slow-wave activity. Furthermore, the study showed that there was an abnormal beta-frequency synchronized output from striatum following dopaminergic neurodegeneration. This is likely to be related to the firing of a population of iSPNs, which innervate the GPe. In the same condition of dopamine depletion, the oscillatory firing of GPe neurons are selectively synchronized at beta frequencies (Mallet, Pogosyan, Marton, et al., 2008). In the pathological network state of dopamine depletion, the iSPNs neurons which are typical GPe neurons are characterized by anomalous fire around the peaks of cortical beta oscillations (Mallet, Pogosyan, Marton, et al., 2008). In light of the results of Sharott's study, the GABAergic iSPNs are the principle generator of exaggerated beta oscillations in BG circuits in the dopamine-depleted state. Indeed, these group of neurons have the tendency to discharge around the frequency of beta oscillations in the condition of a dopamine-depleted striatum (Sharott et al., 2017). This hypothesis is also supported by the anatomical position of GPe neurons, which innervate the GPe and all other BG nuclei (Abdi et al., 2015) and highlights the importance of the GPe-STN network in the generation of pathological beta oscillations in PD. The role of this network in PD has been elucidated in a previous study on dopamine-depleted monkeys (Deffains et al., 2016)

Anatomically, the exaggerated power of the beta oscillation in PD has been linked to an alteration in brain connectivity over the cortico-basal ganglia-thalamo-cortical circuits, disrupted by the dopamine depletion observed in

PD using dynamic causal modelling (DCM) and the 6-hydroxydopamine-lesioned rat model of PD (Moran et al., 2011). These authors found that chronic dopamine depletion reorganised the cortico-basal ganglia-thalamocortical circuit, with increased effective connectivity in the pathway from cortex to subthalamic nucleus (STN) and decreased connectivity from STN to the external globus pallidum (GPe).

This pathophysiological role is confirmed by studies in which either the cortical or subcortical sites have been stimulated in the beta frequency range causing modest but significant slowing of movements. At the cortical level this can be performed non-invasively using tACS. Studies have demonstrated that beta frequency TACS slows movement and markedly reduces the force of errors of commission during no-go trials in healthy subjects (Joundi, Jenkinson, Brittain, Aziz, & Brown, 2012; Pogosyan et al., 2009). These data are complemented by sub-cortical stimulation studies in PD patients in which DBS pulses are delivered at low frequency within the beta range. These have shown a small but significant deterioration in bradykinesia and rigidity in the low frequency stimulation condition (Timmermann & Florin, 2012). Eusebio et al. confirmed that stimulation of the subthalamic nucleus at the beta frequency causes a slowing of movement in patients with PD (Eusebio et al., 2008).

Conversely, successful treatment of PD with levodopa or with subthalamic DBS is associated with a decrease in beta power (Giannicola et al., 2010; Jenkinson & Brown, 2011). It has been showed that levodopa produces remarkable changes in patterns of electrical activity within the STN and basal ganglia. In particular, Giannicola et al. (2010) showed that local field

potentials (LFPs) recorded from implanted DBS electrodes and reflecting presynaptic and postsynaptic activity in large neuronal populations show that STN oscillations respond to levodopa intake in patients with PD. Of note, whereas levodopa abolished the subthalamic beta LFP oscillations in all the patients with PD, DBS decreased beta oscillations only in some patients all of whose LFP recordings already showed high beta activity at baseline. Furthermore, whereas levodopa completely suppressed LFP beta oscillations, DBS merely decreased them. When they combined DBS and levodopa, the levodopa-induced beta disruption predominated the power spectrum, and DBS combined with levodopa induced no significant additive effect (Giannicola et al., 2010).

Additionally, the reduction in beta power in LFP recorded in the STN after administration of levodopa and during continuous high frequency DBS is positively correlated with improvement of motor impairment (Eusebio et al., 2011; Kuhn et al., 2008; Lopez-Azcarate et al., 2010; Oswal et al., 2016; Ozkurt et al., 2011; Trager et al., 2016).

Interestingly Kuhn et al. found that high-frequency stimulation of the STN caused a reduction in LFP beta activity and this was correlated with movement amplitude during a simple motor task. Consequentially, a smaller amount of beta activity was associated with better task performance (Kuhn et al., 2008). Importantly, although current fixed stimulation DBS settings afford good control of motor symptoms in PD, they are also responsible for some side effects. The latter may be related to the indiscriminate suppression or the over-riding of residual physiological functioning in BG-cortical circuits (Eusebio, Cagnan, & Brown, 2012). In addition, Whitmer et

al. showed that DBS may treat Parkinsonism by reducing also excessive synchrony in the functionally connected sensorimotor network through a spatially-specific suppression of beta synchrony in the motor cortex (Whitmer et al., 2012).

In line with this strong evidence, pathologically high amplitude of beta oscillations in PD patients have been proposed as cause of bradykinesia and other motor symptoms (Little & Brown, 2014). However, the mechanism of this effect and proof of the causal relationship between pathological beta activity and motor symptoms of PD is lacking. Several issues remain unresolved, especially the mechanisms by which STN-DBS suppresses beta oscillations. Additionally, other consequences of high-frequency STN-DBS—unrelated to beta suppression—may contribute to symptomatic improvement. Little and Brown proposed that beta oscillations play a key role in normal physiological motor functioning, controlling information coding capacity across the motor loops of the cortico–basal ganglia circuit. Elevated beta activity limits information coding capacity so that novel processing is impaired and the status quo favoured over new movements. This function becomes pathologically exaggerated in PD, resulting in bradykinesia. However, even in PD, the level of beta activity is dynamic, likely fluctuating with moment to moment variations in dopaminergic activity in response to salient internal and external cues. Recognition of this temporal variation lies at the heart of new DBS setting as the closed loop approaches to DBS in PD.

One unresolved aspect of the pathological exaggeration of beta activity in PD is whether beta activity is tonically or phasically elevated. Evidence is

beginning to accrue that physiological beta activity consists of short-lived phasic bursts in basal ganglia-cortical motor circuits (Feingold, Gibson, DePasquale, & Graybiel, 2015; Murthy & Fetz, 1992, 1996) and studies in PD patients undergoing DBS suggest that pathological beta activity may tend to consist of longer duration, phasic bursts (Tinkhauser et al., 2017).

Tinkhauser et al. (2017) showed that levodopa treatment changes the relative distribution of beta bursts in the STN from long to short duration in patients with PD withdrawn from drug treatment, so that there are more long duration bursts OFF compared to ON levodopa. These authors found that beta bursts were much more likely to occur simultaneously and to be phase coupled across hemispheres than by chance in PD patients. Interestingly, clinical correlations were consistent with a deleterious effect of hyper synchronization in long duration beta bursts. The percentage number of longer beta bursts in a given interval OFF levodopa was positively correlated with clinical impairment. On the other hand, the decrease in burst duration after administration of levodopa is also correlated with improvement in motor deficit (Tinkhauser et al., 2017). Okzan et al. (Ozkan, Johnson, Sehirli, Woodhall, & Stanford, 2017) provide in vitro evidence for the differential modulation of beta, theta and gamma activity in M1 by dopamine acting at receptors exhibiting conventional and nonconventional d dopamine pharmacology. The authors showed that dopamine increased beta power. Additionally, the authors showed that dopamine mediates complex actions acting at dopamine D1-like and D2-like receptors, α1 adrenergic receptors and possibly dopamine/α1 heteromultimeric receptors to differentially modulate theta and gamma activity in M1 (Ozkan et al., 2017). Other studies explored the role of other monoamines on the beta

cortical oscillations. Interestingly, Baker & Baker tested the effects of the beta-adrenergic agents propranolol (non-selective beta-agonist) and salbutamol (beta2-agonist) on the cortical oscillations. The authors showed that beta-adrenergic stimulation increased alpha power but it had no effect on beta power (M. R. Baker & Baker, 2012).

1.2 Sensory attenuation phenomena: is it the neurophysiological mechanism underlying modulation of beta oscillations?

Sensory attenuation (SA) is a sensory phenomenon that occurs during active movement. SA was the other neurophysiological mechanism in PD that I studied during my PhD.

It is well known that voluntary movement stimulates peripheral sensory receptors that activate neurons in the cortex via ascending sensory pathways. However, not all of these afferent signals generated during voluntary movement influence the cortical neuronal activity in the same way and they are known to be heavily modulated by top-down signals. Most notably these sensory signals are attenuated during active movement. This SA, also called sensory gating, is well documented and is most commonly believed to reflect an active suppression or cancelation of the predicted sensory consequences of an action so as to make the system more sensitive to unexpected sensations. Somato-sensory evoked potentials (SSEPs) have been employed as a neurophysiological measure of SA. SSEPs represent neural responses to somatosensory stimuli recorded using electroencephalography (EEG). SSEPs reflect the electrical activity of summated post-synaptic potentials from activation of neural structures along the somatosensory pathway (M. X. Cohen, 2017).

Upper limb SSEPs are typically elicited using electrical or mechanical stimulation of peripheral nerves (PN), including the digital nerves in the fingers, or radial, ulnar or median nerve (MN) in the wrist or arm. While SSEPs can be elicited by mechanical stimulation, electrical stimulation of PN, which gives larger and clearer responses, are most often used.

Recording electrodes are placed on the scalp as well as occasionally over the spine, Erb's point, and over PN proximal to the stimulation site. SSEPs recorded from electrodes on the scalp can measure both local electrical activity near the recording electrode (i.e. near-fields) and from more distal locations including the SC (i.e. far-fields) due to volume conduction (Aminoff & Eisen, 1998). Several parameters of SSEPs can be measured, including peak latencies, absolute peak amplitudes or peak-to-peak amplitudes, and waveform morphology (Aminoff & Eisen, 1998). The latency of SSEPs can also be used to measure the peripheral or central conduction time. Peak latencies tend to be consistent across subjects and marked differences likely represent pathological changes related to somatosensory transmission. Absolute peak and peak-to-peak amplitudes of SSEP components are thought to represent the amount of electrical activity related to somatosensory processing at given latencies and are more consistent during repeated SSEP recordings in the same subject (Aminoff & Eisen, 1998). SSEP components typically are named by their negative or positive polarity for the peak latency most often observed in the normal population (i.e. N20 is a negative deflection in the EEG waveform usually peaking at 20ms post-stimulus).

Gating or suppression of SSEPs around the onset of a voluntary movement is a well described physiological phenomenon (Rushton, Rothwell, & Craggs, 1981). Recent studies in primates have suggested that there may be different components to the SSEP suppression, with an important component relating to 'top down' suppression of afferents via the motor cortex (Seki & Fetz, 2012). Interestingly, a greater magnitude of SSEP suppression was associated with faster reaction times in these experiments,

suggesting a link between effective SSEP suppression and improved motor performance (Murase et al., 2000). There is also a peripheral component to SSEP gating/suppression, as it also occurs to an extent during passive movements (Rushton et al., 1981). Interestingly, SSEPs driven by MN stimulation are attenuated during (Murase et al., 2000) and just prior to active movement (Starr & Cohen, 1985). This neurophysiological attenuation in sensory responses during voluntary movement are also believed to affect the sensory percept. The perceptual SA studied from behavior has been proposed as an implicit measure of the sense of agency for movement (Shergill, Bays, Frith, & Wolpert, 2003).

In other words, SA describes a phenomenon associated with normal movement where there is a different perception of identical sensory inputs depending on whether they are self-generated or externally generated. Stimuli which are self-generated are associated with a reduction in the perceived intensity of the stimulus; for example, while one cannot tickle oneself, one can be tickled by others (Blakemore, Wolpert, & Frith, 1998). Furthermore, the phenomenon can also be more easily quantified using a force estimation task. Starr et al showed that healthy subjects tend to overestimate the force required to match a test force when they press on themselves (Starr & Cohen, 1985). Previous accounts of sensory gating have largely interpreted this effect as arising from the active cancellation of a predictable sensory event. However, there are a number of experimental results that are not consistent with this account (H. Brown, Adams, Parees, Edwards, & Friston, 2013). Most notable is the fact that SSEPs are themselves attenuated. SSEPs are the response to an unpredictable somatosensory event and therefore, if the cancellation model were true,

then the SSEPs driven by MN stimulation should be at least the same during static and active movement. However, the SSEPs are attenuated during active movement. This suggests that rather than being an active cancellation of predictable sensory events sensory gating/attenuation is more a global phenomenon during active movement. Indeed, consistent with this recent neurophysiological data in the macaque monkey has demonstrated that sensory gating is largely a global effect occurring both cortically and in the spinal cord (Seki & Fetz, 2012).

Cebolla et al. demonstrated that concomitant finger movements of the stimulated hand counteract with the phase-resetting of the ongoing beta/gamma EEG oscillations and abolishes the N30 component throughout their large topographical extent on the scalp (Cebolla et al., 2009). This finding supports the hypothesis that the phase-locking phenomenon is one of the main generators of the N30 and suggests the involvement of neuronal populations of the sensorimotor cortex and related areas. Indeed, these cortical areas are unable to respond to the phasic sensory activation and to phase-lock their discharges to the external sensory input during the movement.

Interestingly, sensory gating has been found during mental imagery of movement. Indeed, suppression of N30 and P25-N33 complex have been showed during mental movement simulation activity involving the stimulated limb (Cebolla, Palmero-Soler, Dan, & Cheron, 2014; Cheron et al., 2000). Unlike imagery, observation of grasping or performing a sequence of finger movements results in enhancement rather than gating (Cebolla et al., 2014; Cheron et al., 2000; Rossi et al., 2002) supporting the hypothesis that the

mirror neuron system facilitates somatosensory input. Cebolla et al. found that potentiation of frontal N30 while observing another person's hand movement involved the contralateralparietal cortex (Cebolla et al., 2014). The increase in N30 SSEP was concomitant with increases in alpha and beta power while the high-beta gamma was unaffected. These authors showed that the angular gyrus (BA39) exerted a top-down influence on the somatosensory processing indexed by this amplitude potentiation (Cheron et al., 2000). Thus, these findings suggest that observation, unlike active movement, does not disrupt the phase-resetting of the high beta-low gamma oscillations responsible for the N30 SSEP, supporting the idea that different oscillatory mechanisms can be responsible for SSEP amplitude decreases and increases observed in the time-domain.

As highlighted, the SSEP component most often reported in sensory processing for movement control is the frontal N30 (Cebolla et al., 2014; Cheron et al., 2000). The N30 SSEPs likely represent early somatosensory input into non-primary motor areas (Kanovsky, Bares, & Rektor, 2003) with potential oscillatory contributions from M1 and prefrontal cortex (Cebolla et al., 2014) that are distinct from N20 and P27 primary somatosensory cortex (S1)-generated components. In addition to the gating effects on the frontal N30 (Cheron et al., 2000), previous studies also showed that the frontal N30 can be increased during movements contralateral to MN stimulation (Cheron et al., 2000). More recent work revealed that only execution of repetitive non-dominant rather than dominant hand movement results in frontal N30 enhancement (Legon, Dionne, Meehan, & Staines, 2010). However, Brown and Staines (M. J. Brown & Staines, 2015a, 2015b) recently showed a specific modulation of frontal N30 SSEPs during different

time periods (pre-stimulus, early response selection, late movement preparation and movement execution) when individuals prepared and executed contralateral dominant-hand finger sequences that were cued by somatosensory input (vibro-tactile stimuli) at an attended index finger (Fig.1.2.1).The authors found that frontal N30 peak amplitudes were enhanced during the late stages of preparing movement sequences with the contralateral dominant hand around 750 ms after attended somatosensory stimuli cued movement (Fig. 1.2.1) (M. J. Brown & Staines, 2015b).

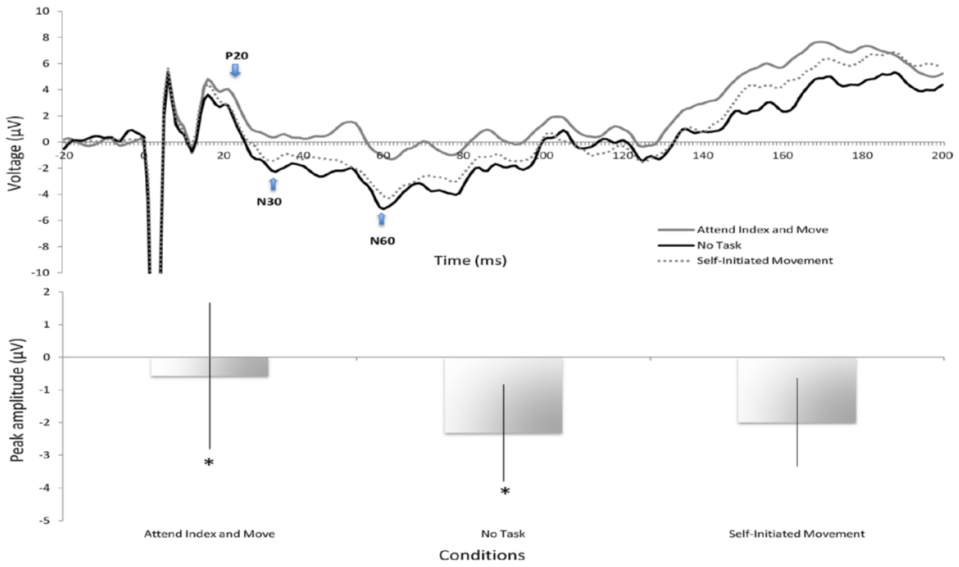


Figure 1.2.1. Frontal SSEPs elicitated by median nerve stimulation. *The top part of the figure shows the grand-averaged (n = 10) waveform (microvolts, uV) of frontal SSEPs elicitated by median nerve stimulation. The bottom part shows theN30 mean peak amplitudes (with standard deviation) at FCz electrode. The data compared the effects of receiving high and low vibrotactile (VibT) stimuli to the left index finger in 3 conditions: during the production of a pre-matched button-press sequence with the right hand (contralateral hand to MN stimulation) (attend Index and move condition), during the production of one of the two button-press sequences approximately every 5 s (self-initiated movement condition), or in absence of movement (no task conditions). Asterisks denote significant differences between conditions. These results support a role of sensory gating of early frontal SSEPs during finger sequence preparation of the limb contralateral to median nerve stimulation that may result from increased activity in prefrontal, motor preparatory areas, and basal ganglia) (M. J. Brown & Staines, 2015b).*

In contrast, frontal N30 SSEPs can be gated during early phases (~250ms after stimulus) of cued contralateral dominant-hand finger sequence preparation (Fig 1.2.2) (M. J. Brown & Staines, 2015a).

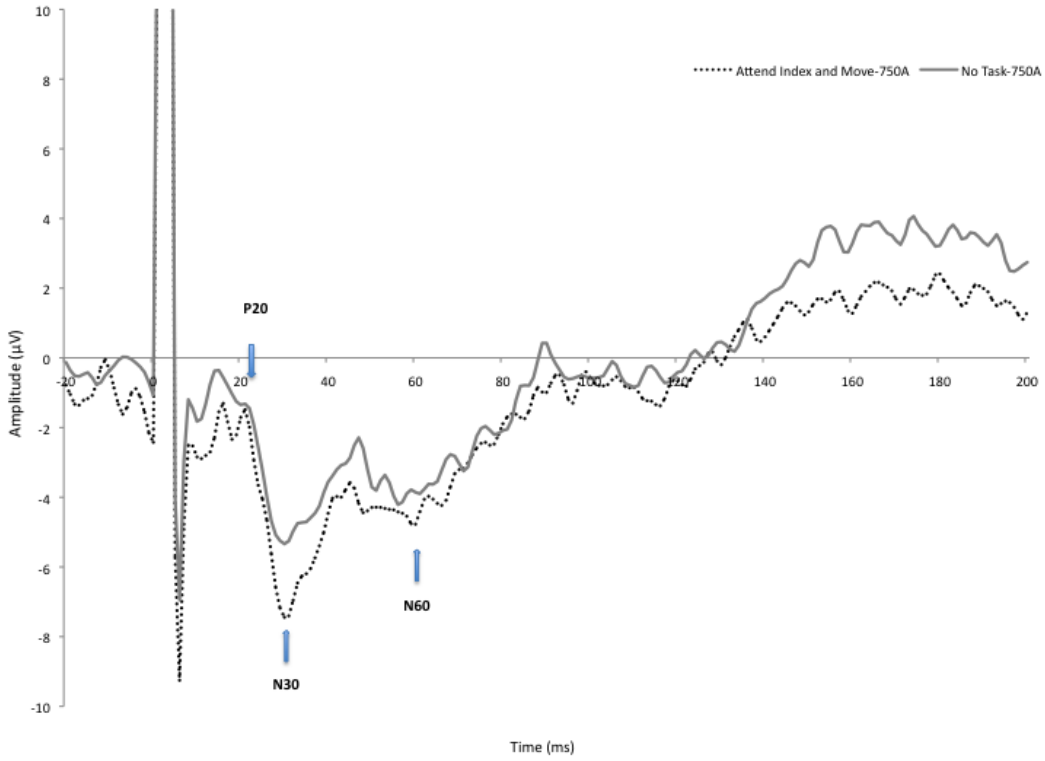


Figure 1.2.2. Frontal SSEPs recording and vibrotactile stimulations*. Grand-averaged (n = 10) waveform in microvolts (μV) at FCz electrode comparing the effects frontal SSEPs measured from left median nerve (MN) stimulation ~750 ms after (750A) vibrotactile (VibT) stimulations to the left index finger between 'Attend Index and Move' and 'No Task' conditions. This result supports the hypothesis that increases in frontal N30 amplitudes during contralateral movements are dependent on the complexity of preparing and executing finger sequences, which is associated with increased activity in several neural areas such as the non-primary motor areas, prefrontal cortex and BG. Furthermore, enhanced N30 SSEPs during contralateral movement preparation and execution may be a necessary mechanism to decrease sensory gating to facilitate somatosensory processing in non-primary motor areas when there is a 'noisy' environment. (M. J. Brown & Staines, 2015a).*

However, no studies have examined how contralateral movements influence the oscillatory generators of the frontal N30. It is speculated that contralateral movement involves disruption of the beta/gamma phase re-setting that has been observed with ipsilateral movements (Cebolla et al., 2009). Collectively, these findings support the idea that SSEPs can be attenuated during movement preparation, regardless of whether movement occurs in dominant or non-dominant, or contralateral or ipsilateral limb to stimulation. It also supports the hypothesis that enhancement of SSEPs such as the N30 may be a necessary mechanism to disinhibit mechanisms of sensory gating to facilitate somatosensory processing in non-primary motor areas in a 'noisy' environment.

Overall, these novel studies highlight the usefulness of SSEPs for measuring changes in somatosensory processing during different phases of movement. Furthermore, the modulation of SSEPs is also highly dependent on which limb is prepared or moved as well as the complexity of the movement. In this context, understanding the neurophysiology of normal movement sensorimotor integration is a primary challenge in current translational neuroscience. Indeed, a thorough understanding of these normal mechanisms can assist in determining specific elements that are disrupted in pathological movements. Interestingly, Insola et al. (Insola, Le Pera, Restuccia, Mazzone, & Valeriani, 2004) found that movement of the hand ipsilateral to MN stimulation gated the triphasic negative-positive-negative 14-18-22.5 ms potential recorded from the STN, similar to scalp-recorded N20, P20 and N30 SSEPs. Similar behaviour of this triphasic complex was observed in two patients in the GPi (Insola et al., 2004). In a recent study (Insola, Padua, Mazzone, & Valeriani, 2015) gating of the

scalp-recorded N20, P20 and N30 SSEPs in addition to triphasic 14-18-22.5 ms complex recorded from DBS electrodes in STN, PPN or VIM was demonstrated with passive movements ipsilateral to MN stimulation. The sensory gating was greater for scalp compared to DBS-recorded SSEPs (Insola et al., 2015).

Active movement has also been found to gate the N30 SSEP recorded from depth electrodes in the dorsolateral premotor cortex (areas 6 and 8) while mental movement gated N30 SSEPs recorded from SMA (Kanovsky et al., 2003). Therefore, these results show that subcortical as well as cortical activity can contribute to SA effects. Inhibition or facilitation appears highly dependent on movement phase and task-complexity and is associated with increased activities in several neural areas including contralateral primary motor cortex, non-primary motor areas (SMA, PMC), prefrontal cortex and basal ganglia. Future experiments using oscillatory models can help clarify the mechanisms involved in these phenomena of sensorimotor control.

1.3 The active inference framework

A recent theoretical account, active inference, has been proposed where sensory attenuation prior to and during active movement is a thought to be an essential step in actually being able to move.

This model of motor control proposes that the brain has to recognize when sensory information is uncertain and has to down weight these external sensations in order for top-down predictions to prevail (K. J. Friston, Daunizeau, Kilner, & Kiebel, 2010). The ensuing active sampling or inference is mandated by ergodic arguments based on the very existence of adaptive agents. Furthermore, it accounts for many aspects of motor behavior; from retinal stabilization to goal-seeking (K. J. Friston et al., 2010). In particular, this model suggests that motor control can be understood as fulfilling prior expectations about proprioceptive sensations. This formulation can explain why adaptive behavior emerges in biological agents and suggests a simple alternative to optimal control theory (K. J. Friston et al., 2010). According to active inference, movements are allowed by the transition from one sensory state to another. The active inference framework is based on the notion that "perception and behavior can interact synergistically, via the environment" to optimize behavior (K. Friston, Mattout, & Kilner, 2011). Motor control in the active inference model is thought as a network where predictions of proprioceptive signals are fulfilled by peripheral motor reflexes (H. Brown, Friston, & Bestmann, 2011). If it is true that action is driven by proprioceptive prediction errors in exactly the same way that perception is driven by exteroceptive prediction errors (K. J. Friston et al., 2010), this means that attentional modulation may operate at

low levels in the motor system in the same way that it operates in the early visual system. Brown's findings support the hypothesis that attentional modulation may enable of top-down predictions of proprioceptive input (H. Brown et al., 2011). Especially, attention enters this picture through context or state-dependent optimization of the precision of prediction errors.

Within this framework sensory attenuation is necessary for movement initiation. Attenuation of the somatosensory input is a necessary consequence of reducing the precision (synaptic gain) of sensory evidence during movement to allow the expression of the prior beliefs that incite movement. One consequence of this framework is that in order to be able to move the prediction errors about the hidden states must be greater than the prediction errors about the somatosensory expectations. In other words, in order to be able to move the gain of the somatosensory prediction error signal must be reduced and this results in the observation of sensory attenuation during active movement. In summary, sensory attenuation can be understood as the attenuation of sensory precision as it has been clearly explained in the new framework proposed by Palmer et al. (C. Palmer, Zapparoli, & Kilner, 2016)

1.4 The relationship between Parkinson's disease and sensory attenuation in the contest of active inference.

Of particular interest is that within the active inference framework a failure to move can be modelled by a failure to sufficiently attenuate precision on the somatosensory expectations (K. J. Friston et al., 2012). Indeed, it has been proposed that some of the hypokinetic symptoms of PD, specifically akinesia and bradykinesia, which are due to an impairment in movement initiation, can be recast as a result of a pathology in reducing the precision of the somatosensory expectations. It is well known that dopamine is a neurotransmitter involved in several areas of neuroscience. It has a wide variety of cognitive and motor functions. In this framework, the attenuation of the precision has been proposed to be mediated by changes in dopamine (K. J. Friston et al., 2012). This means that changing the levels of dopamine changes the level of uncertainty about different representations. In other words, dopamine reports the precision or salience of sensorimotor constructs (representations) encoded by the activity of the synapses they modulate. This leads to a view of dopaminergic projections that select salient processing channels and associated actions. Physiologically, this is compatible with short latency dopamine bursts in the basal ganglia that occur after any salient event, whether rewarding or not (Redgrave & Gurney, 2006).

In summary, dopamine controls the precision or salience of (external or internal) cues that engender action in this account. Therefore, it balances bottom-up sensory information and top-down prior beliefs when making hierarchical inferences (predictions) about cues that have affordance. Put

simply, hypokinetic movement disorder symptoms, which are caused by a dopamine deficit, could arise from a failure in estimating the correct level of sensory precision (K. J. Friston et al., 2012).

This results in a novel and exciting hypothesis to explain the hypokinetic motor symptoms of PD. Within this framework sensory attenuation is realized through a modulation in the synaptic gain of the somatosensory prediction error units. However, what the neurophysiological correlates of this change in precision are remains unknown.

An important challenge in neuroscience is investigating maladaptive plasticity as a neurophysiological mechanism underlying neurological diseases, particularly movement disorders. Several authors have measured abnormal plasticity changes in clinical populations through changes in SSEPs amplitude. Indeed, parkinsonian patients demonstrated a reduction and even, periodically, an abolishment of frontal N30 SSEPs to MN stimulation at rest, although this effect has not been universally found (Abbruzzese & Berardelli, 2003; Cheron, 1999). There is evidence that the N30 SSEP amplitude increased with apomorphine, L-dopa and bilateral STN or GPi DBS in patients with PD (Abbruzzese & Berardelli, 2003; Cheron, 1999). Therefore, the frontal N30 SSEP may represent a dopamine-dependent physiological marker of basal ganglia modulation of the cortical generators of SSEP (Cheron, 1999). This notion is supported by the finding that individuals with Huntington's disease also have reduced or absent frontal N30 SSEPs (Abbruzzese & Berardelli, 2003). In contrast, patients with dystonia, including patients with writer's cramp, demonstrated increased N30 SSEPs at rest (Abbruzzese & Berardelli, 2003). This

neurophysiological change was found in cervical dystonia patients and writer's cramp patients (Kanovsky et al., 1998). Interestingly, the frontal N30 SSEP was absent bilaterally in two young children with striatal lesions (Kato et al., 2007). Collectively, these studies support the hypothesis of a modulatory role of the basal ganglia on the generators of the frontal N30 SSEP. Abnormal sensory gating has been associated with abnormal movement control in various disorders including dystonia and bradykinetic disorders such as PD (Abbruzzese & Berardelli, 2003; Cheron, 1999).

Taken together these studies indicate that the utility of SSEPs recording in different timing of active movements. Indeed, SSEPs at the onset of movement rather than in the later tonic phase of movement may reflect different aspects of sensorimotor integration and plasticity changes related to neurological disorders with the former being more relevant to sensory predictions relating to upcoming movement or change in state of the system between rest and movement. Interestingly, exaggerated beta oscillations (in the 15-30 Hz) within basal ganglia nuclei (e.g. STN and GPi) that reduce with movement and L-dopa have been associated with the bradykinesia in PD (P. Brown, 2006). Specifically, abnormal synchronization of beta oscillations between STN and GPi nuclei within the basal ganglia has been linked to the exaggerated beta oscillations in PD (Mallet, Pogosyan, Marton, et al., 2008). It is known that phase-resetting of high beta-gamma oscillations is responsible for the N30 SSEP at rest (Cebolla, Palmero-Soler, Dan, & Cheron, 2011; Cheron et al., 2007) and could suggest that the changes in cortical N30 SSEP in PD are associated with decreased cortical high beta-low gamma oscillations in association with the exaggerated basal ganglia beta oscillations.

N20-P25 is the other important SSEPs component in sensory-motor integration and elicited by MN stimulation. N20 indicate a negative deflection peaking over contralateral parietal electrodes sites at 19-20 ms post stimulation. P25 is the positive deflection peaking over frontal electrodes around 25 ms post-stimulation. There is a consensus that parietal N20 and frontal P25 potentials represent the earliest cortical potential elicited by MN stimulation and reflect the activity of a dipolar generator in Brodmann's area 3b, tangent to scalp surface and situated in the posterior bank of the Rolandic fissure (Broughton, Rasmussen, & Branch, 1981). A P22 recorded in the central region was found to peak 1-2 ms later than the N20-P20 potentials in parietal region. The question whether the radial source of the central P22 is located behind the central sulcus, in the primary somato-sensory area, or in front of it, in the primary motor area, was not easy to address. However, dipole modelling studies of SSEPs using realistic head models supported the view that the P22 source is located at the crown of the post-central gyrus (Buchner et al., 1996). Here, my research was particularly focused on the N20-P25 amplitude as measure of SA.

1.5 Vibratory stimulation and motor performance

Muscle proprioceptive information is known to be of prime importance in the sense of posture and movement, and in the motor control (Roll & Vedel, 1982; Windhorst, 2007). In the 1960s, Matthews as well as Hagbarth performed animal and human experiments showing that vibration applied to the muscular tendon system can elicit a reflex muscle contraction labelled as “tonic vibration reflex” (TVR) (Hagbarth & Eklund, 1966; Matthews, 1966). The TVR is seen with high frequency mechanical vibration, which induces a contraction of human skeletal muscle and relaxation of its antagonists. This TVR is physiologically related to the excitation of primary spindle endings. Indeed, mechanical vibration applied to muscle tendons activate the muscle spindle primary endings strongly and, consequently, the vibratory stimulation on the stretched muscle during movement induces an increase in proprioceptive activity (Roll, Vedel, & Ribot, 1989). Hagbarth and colleagues showed that the strength of this reflex varies with the parameters of the vibration and with the initial state of contraction and length of the muscle vibrated (Hagbarth & Eklund, 1966). The vibratory stimulation activates muscle spindle afferents, primary endings, where the muscle feedback is not only related to the movement performed, but also to the vibration-induced response (Roll et al., 1989). Several studies showed evidence that that vibratory stimuli have multiple actions on a wide variety of physiological functions as brain activation, hormone concentrations and neurotransmitter releases (Ariizumi & Okada, 1985; Boecker et al., 1999; McCall, Grindeland, Roy, & Edgerton, 2000; Nakamura, Moroji, Nagase, Okazawa, & Okada, 1994; Nakamura, Moroji, Nohara, Nakamura, & Okada, 1992). These studies also highlight that different vibration characteristics

(whole-body vs. local) and parameters (as frequency and amplitude) influence these effects strongly.

Proprioception is an important component of motor control and the influence of vibrations have been studied in a number of studies. Regardless of whether vibrations were applied locally to various muscles or to the whole-body, a prominent influence on motor control is evident (Bove, Diverio, Pozzo, & Schieppati, 2001; Goetz, Leurgans, Raman, & Parkinson Study, 2002; Ivanenko, Grasso, & Lacquaniti, 2000a, 2000b; Ivanenko, Talis, & Kazennikov, 1999; Verschueren, Swinnen, Cordo, & Dounskaia, 1999a, 1999b; Verschueren, Swinnen, Desloovere, & Duysens, 2003; Wierzbicka, Gilhodes, & Roll, 1998).

Several authors investigated the effect of vibrations applied to various muscles during walking on the velocity and the direction of gait. In particular, it has been shown the involvement of Ia afferent input in the control of muscle activity during gait (Verschueren et al., 2003) as well as at postural level, mainly in the anterior-posterior direction (Wierzbicka et al., 1998).

Interestingly, neck muscle vibration during gait produces trajectory deviation related to its effect on stance (Bove et al., 2001). However, vibration before locomotion was found to cause a major deviation from the planned trajectory, this is likely to be due to a disorientation of the internal references (Bove et al., 2001). Notably, Ivanenko and colleagues found that continuous neck vibration caused changes in the postural reference during quiet standing and in the walking speed during locomotion. Their results suggested the important role of proprioceptive input from the neck on the control of human posture and locomotion. The authors suggested that it is

processed in the context of a viewer-centred reference frame (Ivanenko et al., 2000b).

Vibration of Achilles tendons and of neck dorsal muscles influence the postural responses in different modalities reflecting the participation of different muscles in posture control (Ivanenko et al., 1999). Ivanenko and collaborators tested the effect of vibratory stimulation of the following leg muscles: bilateral quadriceps (Q), hamstring (HS) muscles, triceps surae (TS), and tibialis anterior (TA). Vibration of thigh muscles altered the walking speed depending on the direction of progression. During backward locomotion, the walking speed tended to decrease after HS vibration, whereas it significantly increased after Q vibration. These results suggested that the proprioceptive input from thigh muscles may convey information about the velocity of the foot movement relative to the trunk (Ivanenko et al., 2000a).

Verschueren and colleagues tested whether proprioception is used by the central nervous system to control the spatial and temporal characteristics of unimanual circle drawing (Verschueren et al., 1999b) as well as bimanual circle drawing (Verschueren et al., 1999a). Tendon vibration caused distortions to the unimanual circle drawing suggesting that the central nervous system uses proprioceptive information to accomplish the spatial characteristics of this motor task (Verschueren et al., 1999b). Interestingly, the spatial characteristics of circle drawn by the vibrated arm during the bimanual experiment were found to be affected by tendon vibration in a way similar to the unilateral task. These results suggested that the spatial characteristics of hand movement are controlled unilaterally. Whereas the

temporal characteristics of movement measured by interlimb coupling appeared to be controlled by proprioceptive information from both limbs, possibly by a proprioceptive triggering mechanism (Verschueren et al., 1999a).

Several studies have investigated the duration of vibration on the motor performance. In this regard, Wiezbicka and co-workers found that vibration produced long-lasting dynamical modification of posture mainly in the anterior-posterior direction in the studied subjects. These results suggested that sustained Ia sensory inflow, evoked by vibration, has a powerful after-effect on the motor system at the postural level (Wierzbicka et al., 1998).

The influence of vibratory stimuli on the motor performance is labelled ‘kinaesthetic illusion’ and it is physiologically due to a misinterpretation of the vibratory stimulus due to its artificial character. Indeed, in healthy subjects, the increased feedback from the Ia afferents changes the sense of movement. In healthy subjects, this increase in muscle spindle activity is interpreted as if the movement was performed at a higher velocity and this leads to a deceleration and reduced amplitude of the voluntary movement, as compared to the desired movement generating a phenomenon labelled as “a vibration-induced movement error” (Capaday & Cooke, 1981; Cody, Schwartz, & Smit, 1990).

Several experiments have shown that vibration frequencies of more than 20 Hz are necessary to generate kinaesthetic illusions (Cordo, Gurfinkel, Bevan, & Kerr, 1995; Naito et al., 2002). Furthermore, it was found that kinaesthetic illusions are influenced in upright stance by the support stability

(Ivanenko et al., 1999). Consequentially, instable support reduced the degree of illusion and interferes with the results.

1.6 Somatosensory and proprioception deficit in Parkinson's disease

Pathological modified proprioception in PD has been demonstrated in several studies. However, the peripheral muscle feedback seems to be spared in these patients. This was demonstrated by microneurographic recordings of muscle proprioceptive afferents (Hagbarth, Wallin, Lofstedt, & Aquilonius, 1975). On the contrary, the central processing of this sensory feedback is impaired in PD patients as shown by several studies. For instance, PD patients exhibited a higher threshold for detecting passive movements (Konczak, Krawczewski, Tuite, & Maschke, 2007; Maschke, Gomez, Tuite, & Konczak, 2003). Maschke and colleagues demonstrated that in comparison with healthy control subjects, PD patients, but not patients with cerebellar diseases, were significantly impaired in the ability to detect displacements correctly. This study has been particularly important because it highlighted the selective role of basal ganglia, and not the cerebellum, in the conscious awareness of limb position (kinaesthesia) (Maschke et al., 2003). Consequentially, these results confirmed previous findings showing that dysfunction of the basal ganglia leads to proprioceptive deficits (Schneider, Diamond, & Markham, 1986, 1987). Previously, Zia and colleagues showed that patients with PD were impaired in unilateral elbow-joint position sense (Zia, Cody, & O'Boyle, 2000; Zia, Cody, & O'Boyle, 2002). Neurophysiological evidence for impaired processing of proprioceptive stimuli in basal ganglia came from a study investigating proprioception-related EEG potentials elicited by passive movements in Huntington's disease and PD patients (Seiss, Praamstra, Hesse, & Rickards, 2003). Indeed, early proprioception-related potentials (N90) were normal in these patients, but alterations in longer latencies

(~170±180 ms) were most likely due to disease-specific changes in cortical processing of kinaesthetic signals. Boecker et al. confirmed the abnormal cortical and subcortical activation on passive sensory stimulation in PD as well as HD (Boecker et al., 1999). Taken together, these studies showed that the sensory input to the basal ganglia is used not only for movement feedback and sensorimotor integration but also for the discrimination of somatosensory stimuli that leads to the awareness of limb motion and, thus, are responsible of the kinaesthesia phenomenon. If the basal ganglia can be considered a sensory analyser for motor control (Lidsky, Manetto, & Schneider, 1985), then PD as well as other movement disorder would be the result of a primary sensory dysfunction that causes faulty computation of relevant movement parameters. Konczak et al. found that the detection of passive motion is impaired in PD (Konczak et al., 2007). In particular, PD patients needed larger limb displacements and required more time before they could judge the presence of passive motion. Interestingly, this deficit seemed to affect patients at early stages of their disease. In addition, it has been shown that there are proprioception deficits in PD in the localization errors in hand position during matching tasks (Lee, Henriques, Snider, Song, & Poizner, 2013). Interesting, it was found that STN-DBS improved proprioceptive accuracy in limb localization, but reduced its precision (Lee et al., 2013). Interestingly, the proprioceptive deficit in PD appears to be central rather than peripheral in origin, since muscle spindle function and early cortical processing of proprioceptive information is essentially unaffected in PD, but later cortical processing is impaired (Seiss et al., 2003).

Changes in the cerebro-basal ganglia loop are thought to be responsible for the altered proprioceptive integration seen in PD (Maschke et al., 2003). It is well known that vibratory stimulation activates muscle spindle afferents, particularly primary endings (Roll et al., 1989), where the muscle feedback is not only related to the movement performed, but also to the vibration-induced response. In healthy subjects, this increased feedback changes the sense of movement, where the subject has an impression that the movement was performed at a higher velocity, leading to a reduction in the amplitude of the desired movement and a vibration-induced movement error (Capaday & Cooke, 1981; Cody et al., 1990). In PD patients, this vibration-induced error is decreased, which indicates an altered processing of proprioceptive sensory information (Khudados, Cody, & O'Boyle, 1999; Rickards & Cody, 1997). Changes in the supraspinal processing of proprioceptive input in PD have been demonstrated by analyzing the effect of mechanical vibration applied to the tendon of a muscle stretched during voluntary movements (Khudados et al., 1999; Rickards & Cody, 1997). In this regard, Rickards and Cody found significant lower undershooting errors in PD patients compared to healthy subjects during voluntary wrist extension movements and vibration transfer to the flexor carpi radialis (Rickards & Cody, 1997). Khudados et al. showed comparable low impacts of vibrations on tracking performance in PD compared to age matched controls (Khudados et al., 1999). Overall, the defective utilization of such proprioceptive information contributes to the movement issues that characterize this disease in terms of movement control as well as postural control (Vaugoyeau & Azulay, 2010; Vaugoyeau, Viel, Assaiante, Amblard, & Azulay, 2007). Indeed, axial proprioception is impaired as well as limb

proprioception (Wright et al., 2010). Thus, any therapy that could alleviate kinaesthetic deficits may be considered important in the treatment of these patients (Maschke, Tuite, Pickett, Wachter, & Konczak, 2005). Several studies have examined whether dopaminergic therapy reverses proprioceptive deficits in PD, but the results are conflicting. Of note, dopaminergic therapy acutely worsened limb proprioception (O'Suilleabhain, Bullard, & Dewey, 2001). Mongeon and colleagues likewise found that it worsened limb proprioception, but only in some patients (Mongeon, Blanchet, & Messier, 2009). In contrast, Maschke et al. found that dopaminergic therapy had no effect on limb proprioception (Maschke et al., 2003), while Li and collaborators found that it improved limb proprioception (Li, Pickett, Nestrasil, Tuite, & Konczak, 2010). Even less is known about the effects of deep brain stimulation of the STN-DBS on proprioception. It was found that STN DBS produced a small but significant improvement in proprioceptive acuity in a task in which patients' had to detect passive forearm displacements (Maschke et al., 2005).

1.7 The impact of vibration on motor signs in Parkinson's disease

PD is typically treated pharmacologically with levodopa and dopaminagonist. However, over time patients report an increasingly shorter period of symptom relief with these medications and develop a wide array of psychiatric and motor impairments (Rao, Hofmann, & Shakil, 2006). The studies on the efficacy of both occupational and physiotherapy have been conflicting (Deane, Jones, Playford, Ben-Shlomo, & Clarke, 2001; Dixon et al., 2007). Therefore, several researchers have explored alternative non-pharmacologic strategies to relief the symptoms of PD. In this regard, several evidences have supported a positive impact of vibration therapy as a prospective approach for improving symptoms in PD (Haas, Turbanski, Kessler, & Schmidtbleicher, 2006) by influencing the abnormal neural rhythms associated with the disease. Indeed, it is well known that the basal ganglia in PD patients are held abnormally in a 15–30 Hz oscillatory rhythm and this is related to the level of dopamine stimulation (Levy et al., 2002). It has been hypothesized that the mechanical perturbations of vibration therapy may disrupt these hyper-synchronized rhythms (King, Almeida, & Ahonen, 2009). Several studies have examined vibration as a potential therapeutic intervention for motor signs of PD, including bradykinesia and resting tremor. Jobges and colleagues administered vibration to single upper limb muscle groups in PD patients affected by moderate resting tremor, and subsequently they found improvement in tremor. The authors suggested that the tremor frequency was influenced by manipulating local sensory feedback to the limb (Jobges, Elek, Rollnik, Dengler, & Wolf, 2002). On the contrary, Haas et al. investigated the effects of vibration using variable stimuli on the whole body of PD participants rather than single

muscle groups (Haas et al., 2006). The authors used random stimuli following Schultz's results, which showed that unpredictability of a stimulus is directly related to dopamine release (Schultz, 1998). Interestingly, Haas et al. delivered random unsynchronized vibration (varying in amplitude) to the feet of PD participants from a platform and the effects was experienced throughout the whole body (Haas et al., 2006). The authors found a highly significant improvement of 16.8% in the Unified Parkinson's Disease Rating Scale (UPDRS) motor score (tremor and rigidity scores improved by 25% and 24% respectively). King et al. used physio acoustic vibration on PD patients, to ensure uniform delivery of stimulation to the entire body. The authors found a significant relief in terms of rigidity and resting tremor in their cohort of participants (King et al., 2009). In the clinical practice, numerous PD patients report that symptoms are markedly reduced in vibratory situations e.g. train travelling. Consequentially, several authors have tried to investigate and develop device generating vibration which can improve motor symptoms in PD.

Chapter 2. SCOPE OF DISSERTATION AND HYPOTHESES

The aim of the work proposed in this thesis is to test a novel theoretical account of movement and movement disorders, in order to test whether this account can explain some of the hypokinetic symptoms observed in PD. In particular, this research tested a theory of the functional role of sensorimotor beta oscillations that could explain beta power modulations in healthy subjects and the increase in beta power observed in PD patients. Furthermore, I tested if beta oscillations are causally linked to the imprecision or demodulation of proprioceptive predictions. In other words, the aim was to combine experimental and theoretical research with novel data analyses to test predictions of the active inference framework, specifically to test whether this framework can explain the hypokinetic movement disorders of PD.

Specifically, I investigated the prediction that modulations in precision are causally correlated with modulations in sensorimotor beta oscillations.

Several observations suggest that there is compelling evidence to predict sensorimotor beta power and estimates of sensory precision might be linked (Fig. 2.7):

1) Sensorimotor beta oscillations are known to be attenuated during motor preparation and execution; active inference would predict a decrease in precision.

2) Increases in sensorimotor beta-power are associated with the inhibition of executed actions; active inference would require an increase in somatosensory precision to inhibit an action.

3) Sensorimotor beta-power is augmented in patients with PD compared to healthy controls; active inference would predict a high level of sensory precision in PD patients compared to healthy controls.

4)The mentioned neurophysiological model of sensorimotor beta-oscillations tested in both health and movement disorders, will be related to models of sensory attenuation in which beta oscillations will be associated with the imprecision or demodulation of proprioceptive predictions.

The aim was to test:

1) Whether a failure of sensory attenuation can account for bradykinesia, the cardinal motor symptom of PD.

2) Whether sensorimotor beta oscillations are causal linked to modulations in precision.

3) Whether bradykinesia in Parkinson's disease can be ameliorated by non-invasive interventions that decrease sensory precision

Furthermore, the thesis aims to explore the possibility to improve motor signs of PD modulating proprioception with vibratory stimulation.

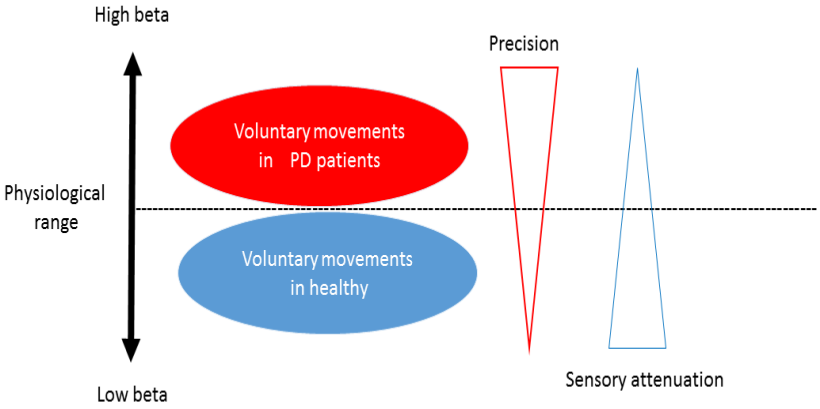


Fig. 2.1 *Network between beta oscillations, sensory precision and sensory attenuation.*

In this section I will describe the aims and motivations for each of the results chapter.

2.1. The role of sensory system in PD: the sensory attenuation at the onset of voluntary movements

I attempted to provide essential evidence on the basic neurophysiological characteristics of sensory input at the onset of the movement. I investigated the relationship between sensory attenuation and onset of voluntary movement in a cohort of normal volunteers as well as patients with PD. The experiment was focused at the onset of an isolated finger movement. I hypothesised that SSEPs will be attenuated less in PD group than in healthy controls. I provided a complete description of the profile of SA by providing descriptive data of N20-P25 at the onset of movement. Such comparisons are an essential first step in exploring the proposal that SA is a mechanism for the correct initiation and performance of voluntary movement and, thus, it might be involved in the generation of bradykinesia in PD.

2.2. Investigating the potential correlation between sensory attenuation and beta oscillations in PD

It is currently well known that beta oscillations generated in the basal ganglia are important for motor control. It is known that PD patients show high beta oscillations in the basal ganglia and this neurophysiological pattern is normalized by the current available therapies (STN-DBS and dopaminergic therapy).

However, although several studies suggest that pathological high amplitude of beta oscillations may cause bradykinesia and other motor symptoms in PD (Little & Brown, 2014), the neurophysiological mechanism of this effect and proof of the causal relationship between pathological beta activity and motor symptoms is still lacking.

In this regard, I aimed to test the hypothesis the two neurophysiological aspects seen in PD (lower SA at the onset of movement and high amplitude of beta oscillations) were correlated.

2.3. Vibratory stimuli, proprioception and Parkinson's disease

Previous studies have provided evidence that patients with PD have impaired proprioception. Here I tested the development of some devices generating vibration to improve the motor signs of PD. Especially, I focused on improvements in bradykinesia symptoms.

In the first approach I used vibration at the right wrist during movement of the right thumb. Then, I used a device around the right wrist during different actions (writing, drawing, holding pen).

I hypothesised that this sensory input would improve the motor performance in PD patients.

Chapter 3. GENERAL METHODS

In this chapter I will describe some of the methods I have employed during my PhD that are common to different experiments. This precise methodological description for each experiment will be described in the relevant results chapters

3.1. Somatosensory evoked potentials

The SSEP is the neuronal response to somatosensory stimuli typically recorded using electroencephalography (EEG). SSEPs reflect the electrical activity of summated post-synaptic potentials from activation of neural structures along the somatosensory pathway (M. X. Cohen, 2017). It is possible to identify SSEPs related to different stages of somatosensory processing including neuronal activation in spinal cord (SC), relay through SC to brainstem and subcortical structures via dorsal-column medial lemniscus (DC-ML) pathway, and cortical structures.

Upper limb SSEPs are typically elicited using electrical or mechanical stimulation of peripheral nerves (PN), including the digital nerves in the fingers, or radial, ulnar or median nerve (MN) in the wrist or arm. Recording electrodes are placed on the scalp as well as occasionally over the spine, Erb's point, and PN proximal to the stimulation site (for detailed review of technical requirements see (Mauguiere et al., 1999). Several parameters of SSEPs can be measured in the traditional time domain, including peak latencies, absolute peak amplitudes or peak-to-peak amplitudes, and waveform morphology (Mauguiere et al., 1999). SSEP latencies can also be used to measure the peripheral or central conduction time. Peak

latencies tend to be consistent across subjects and marked differences likely represent pathological changes in somatosensory transmission (Mauguiere et al., 1999). Absolute peak and peak-to-peak amplitudes of SSEP components are thought to represent the amount of electrical activity related to somatosensory processing at given latencies. SSEP components typically are named by their negative or positive polarity at the peak latency, and the time of the peak latency (e.g. N20 is a negative deflection in the EEG waveform usually peaking at 20ms post-stimulus) and are typically observed in the normal population. The individual latency value for a component may be different from that implied by the component's name (Mauguiere et al., 1999).

Recording of SSEPs has been applied to measure several important neurophysiological changes related to different functions of the somatosensory system. It is a relatively easy to use and inexpensive technique compared neuroimaging methods. Importantly, EEG recordings have two advantages compared to neuroimaging: they provide higher temporal resolution, and a more direct measure of neuronal activity compared to the rather indirect information of blood flow changes in neuroimaging.

3.1.1 Components of SSEPs in sensory motor control

In this section I describe the different components of SSEPs. My work was focused on N20-P25 generated by MN stimulation. The change in amplitude of this component was the measure of SA in my projects.

In the SC and brainstem, SSEPs recorded from the posterior surface of the neck performed by Desdmedt and Cheron (Desmedt & Cheron, 1980) established the different components of spinal and brainstem evoked potentials. The P9 is the first event evoked by MN that has a widespread far-field positivity recorded with the identical latency over the entire scalp, the earlobes and the neck. This component is related to the nerve volley as it enters the brachial plexus from the axilla. N11 is the early negative component recorded over C6-C7 cervical spines. It is generated in the spinal cord near the entry of the afferent nerve volley. The latency of N11 increases at rostral levels of the neck and this has important implications for relating this SSEP component to ascending conduction of the somatosensory volley in the dorsal column. It has been interpreted as a pre-synaptic generator, which ascends the dorsal column. These authors identified the interesting spinal component P13, which has been related to a post-synaptic fixed generator in the central part of the dorsal horn (Desmedt & Cheron, 1980). Of note, the neuronal generator is not a serial link in the somatosensory pathway going up from the spinal entry to the cerebral cortex. Therefore, it is clearly different from the scalp far-field P14 related to the ascending volley in the median lemniscus. These SC and brainstem SSEPs recordings are particularly useful to separate the effects in the SC and brainstem compared to cortical SSEPs.

Intracranial recordings from electrodes placed on or within the cortical tissue have provided valuable information regarding areas that are involved in generating specific SSEPs, including SC and brainstem activities. There is a well-established clinical utility of intracranial SSEPs recordings for localizing S1 or DC-ML pathway during various surgical procedures (Cruccu et al., 2008). Localization of SSEPs is vital for clinicians to localize lesion sites or dysfunction in somatosensory pathway but also provides important information for basic science, including motor control. Unlike surface recordings, intracranial recordings, particularly with depth electrodes, are advantageous due to multiple electrode contacts that can record phase-reversals, and sharp potential gradients (Barba, Valeriani, Colicchio, & Mauguiere, 2008) as well as avoiding reduction and smearing of electrical signals by the skull. Due to the invasiveness of intracranial recordings, these recordings are virtually always performed in patients undergoing surgery or surgical monitoring (i.e. epilepsy or deep brain stimulation patients), and sometimes involved general anaesthesia.

Early, or short-latency, cortical SSEPs to upper limb stimulation have peak latencies in the 18-35 ms range. They are recorded on the scalp in the parietal region and in a large fronto-central area, mostly contralateral to stimulation. N19 and N20 represent a negative deflection beginning around 14 ms and peaking over contralateral parietal electrodes sites at 19-20 ms post stimulation. P20 is the positive deflection peaking over frontal electrodes around 20 ms post-stimulation. There is a consensus that parietal N20 and frontal P20 potentials represent the earliest cortical potential elicited by MN stimulation and reflect the activity of a dipolar generator in Brodmann's area 3b, tangent to scalp surface and situated in

the posterior bank of the Rolandic fissure (Mauguiere et al., 1999). A P22 recorded in the central region was found to peak 1-2 ms later than the N20-P20 potentials in parietal region. Intracranial recordings in M1 showed peak activity as early as 21-22 ms (Balzamo, Marquis, Chauvel, & Regis, 2004), supporting that the P22 could be elicited by activity within M1.

P25, P27 and P30 are positive deflections recorded with electrodes over the contralateral parietal region, their peaking latencies show large inter-individual variations between 23 and 30 ms (Mauguiere et al., 1999). P25 tends to be recorded by more medial parieto-central electrodes and is likely produced by a radial source within area 1 in the primary somatosensory cortex (S1) (Mauguiere et al., 1999). In contrast, P27/P30 represents activity related to a tangential source in Brodmann's area 3b equivalent to the N20 SSEP (Mauguiere et al., 1999). N35 is negative deflection recorded over medial parieto-central electrodes contralateral to stimulation, which likely reflect the same radial source within area 1 of S1 as the P25 (Barba et al., 2008; Hsieh, Shima, Tobimatsu, Sun, & Kato, 1995). Recordings made directly on the cortical surface have verified that the 20 ms negativity recorded in S1 is typically followed by positive peaks between 25-30ms (Barba et al., 2008). Depth recordings in S1 in a few patients revealed a negative SSEP peaking around 36ms at the deepest contacts in addition to the earlier N20/P30 SSEPs and later ~50 and ~100 ms SSEPs recorded with more superficial contacts (Barba et al., 2008). The frontal potential labeled as "N30" is recorded in the frontal region contralateral to the site of stimulation, but it often spreads to the mid-frontal region and to ipsilateral frontal electrodes. Its waveform shows two distinct components with the earlier one peaking at about 24-25ms (N24/N25), and the later at about 30

ms (N30). The N24/N25, and even occasionally N27, can be recorded from frontal electrodes representing the dipoles of the positive parietal potentials. Although there is much controversy over the origin of the frontal N30, specifically as dipole of the parietal component (Barba, Frot, Guenot, & Mauguiere, 2001; Barba, Valeriani, Colicchio, & Mauguiere, 2005; Barba et al., 2003), depth recordings found that the frontal N30 may be locally generated within the SMA as well as the dorsolateral premotor cortex (including both Brodmann's areas 6 and 8) (Kanovsky et al., 2003).

Since excision or lesions of the postcentral cortex preserve frontal SSEPs, it supports that both precentral and postcentral areas receive divergent somatosensory input during the early processing stages. Cebolla et al. (Cebolla et al., 2011) demonstrated that oscillatory generators are also responsible for the frontal N30 component in the frontal cortex. The oscillating generators in alpha, beta and gamma frequencies of the N30 were located in the primary motor cortex (BA4), the premotor cortex (BA6) and the pre-frontal cortex (BA9) (Cebolla et al., 2009). In line with dipole studies, the oscillatory models support the view that the frontal N30 is a unique marker of somatosensory processing.

Collectively, depth recordings have provided supporting evidence that somatosensory information relays in humans between SC, cuneate nucleus, thalamus from 13 ms, 14-16 ms and 16-18 ms, respectively. Once reaching the cortex, S1, M1, S2 and premotor areas such as SMA-proper and pre-SMA, and dorsolateral premotor cortex receive somatosensory input between 20-60 ms. It appears that other subcortical areas such as PPN may also receive somatosensory input between 14-16 ms but it is

unclear if basal ganglia nuclei such as STN and GPi receive input or whether SSEPs recorded from these areas are due to spreading from otherthalamic or cortical generators.

The modulation of SSEPs during different phases of voluntary movements is thought to be the neurophysiological correlate underlying sensorimotor integration, which is an essential component of motor control. Indeed, it is well known that voluntary movement stimulates peripheral sensory receptors that activate neurons in the cortex via ascending sensory pathways. However, not all of these afferent signals generated during voluntary movement influence the cortical neuronal activity in the same way and they are known to be heavily modulated by top-down signals. Most notably, these sensory signals are attenuated during active movement. This phenomenon is called sensory attenuation (SA) or sensory gating as it has been described in the previous chapter.

3.2 EEG

The EEG is a method to record the sum of electrical activities of populations of neurons, with a modest contribution from glial cells. It is well known that neurons are excitable cells with characteristic intrinsic electrical properties, and their activity produces electrical and magnetic fields. These fields may be recorded by means of electrodes at a short distance from the sources (the local EEG or local field potentials, LFPs), or from the cortical surface (the electrocorticogram or ECoG), or at longer distances, even from the scalp (i.e. the EEG, in the most common sense) (Lopes da Silva, 1991).

Neurons generate time-varying electrical currents when activated. These are ionic currents generated at the level of cellular membranes; in other words, they consist of transmembrane currents. We can distinguish two main forms of neuronal activation (Lopes da Silva, 1991): the fast depolarisation of the neuronal membranes, which results in the action potential mediated by the sodium and potassium voltage-dependent ionic conductances gNa and gK, and the slower changes in membrane potential due to synaptic activation, as mediated by several neurotransmitter systems.

Interesting, the action potential is related to a rapid change in membrane potential such that the intracellular potential suddenly jumps from negative to positive, and in 1 or 2 ms returns to the resting intracellular negativity. Regarding the slower postsynaptic potentials, two main types have to be distinguished: the excitatory (EPSPs) and the inhibitory (IPSPs) potentials, which depend on the neurotransmitter and corresponding receptor and their

interactions with specific ionic channels and/or intracellular second messengers.

The neurons that mainly contribute to the EEG are those that form “open fields” according to the classic description of Lorente de Nó (R, 1947). In this regard, pyramidal neurons, when activated with a certain degree of synchrony, generate coherent electric/magnetic fields. In this way, these neurons are akin to “current dipoles”, the activity of which can be detected by electrodes placed at relatively small distances. Different types of rhythmical activities can be recorded from the brain.

In my PhD I was interested in recording beta oscillations, which are brain electrical activity at 15-30 Hz frequency.

The identification and characterization of high-frequency rhythms in the neocortex has concentrated mainly on two neocortical areas, the visual cortex and the somatomotor cortex. I was focused in the somatomotor cortex in my PhD.

In the somato-motor cortex, beta/gamma oscillations of both neuronal firing and LFPs were described in the awake cat (Bouyer, Montaron, Vahnee, Albert, & Rougeul, 1987; Buser & Rougeul-Buser, 2005).

Interestingly, changes in EEG phenomena, particularly in the beta and gamma frequency ranges, that are event-related and reflect a decrease or an increase in the synchrony of the underlying neuronal populations. The former is called event-related desynchronization (ERD), and the latter event-related synchronization (ERS) (Pfurtscheller & Lopes da Silva, 1999). After a voluntary movement, the central region exhibits a localized beta ERS

that becomes evident soon after cessation of the movement. The exact frequency of this rebound beta ERS can vary considerably with the subject and type of movement.

Our understanding of the meaning of ERS of the beta frequency range, which typically occurs after a movement, has been greatly enhanced by the observation that when this form of ERS occurs, the excitability of the corticospinal pathways decreases, as revealed by means of transcranial magnetic stimulation. This supports the hypothesis that the postmovement beta ERS corresponds to a deactivated state of the motor cortex (Lopes da Silva, 1991).

Knowledge of the electrical fields generated by local neuronal networks is of interest to the neuroscientist because these signals can yield relevant information about the activity modes of neuronal populations. Indeed, it is necessary to understand how populations of neurons interact and undergo self-organisation processes to form dynamical assemblies. The latter constitute the functional substrate of complex brain functions(Lopes da Silva, 2013).

Chapter 4. DOPAMINERGIC TREATMENT MODULATES SENSORY ATTENUATION AT THE ONSET OF THE MOVEMENT IN PARKINSON'S DISEASE: A TEST OF A NEW FRAMEWORK FOR BRADYKINESIA.

4.1. Sensory attenuation at the onset of the movements

There is considerable evidence that sensory afferents are attenuated just prior to and during movement (Angel & Malenka, 1982; Milne, Aniss, Kay, & Gandevia, 1988; Rushton et al., 1981; Voss, Ingram, Haggard, & Wolpert, 2006).

An emblematic example of this phenomenon is the impossibility of tickling oneself (Blakemore et al., 1998). This phenomenon, known as sensory attenuation or sensory gating, is most commonly proposed as reflecting an active suppression or cancellation of the predicted sensory consequences of an action so as to make the system more sensitive to unexpected sensations (Blakemore et al., 1998; Rushton et al., 1981; Voss et al., 2006). More recently, a theoretical account, active inference, has been proposed that provides an alternative mechanistic account of this movement-related sensory attenuation (H. Brown et al., 2013). Within the active inference framework, a failure to correctly initiate or maintain movement can be modelled as a failure of adequate sensory attenuation (H. Brown et al., 2011). This raises the question of whether the pathophysiology of this clinical manifestation of bradykinesia in Parkinson's disease (A. J. Hughes, Daniel, Kilford, & Lees, 1992), which is a deficit in movement initiation and maintenance of movement, can be recast as a result of a deficit in sensory

attenuation. If this is the case, then one would predict that sensory attenuation, as measured by the reduction in amplitude of somatosensory evoked potential components at the onset of movement compared with rest, should be reduced in patients with Parkinson's disease (PD) and should improve with medical treatment. Therefore, the aim of the first study of my thesis was to test if patients with PD showed a reduced SA compared to age-matched healthy controls.

4.1.1. Methods

Eighteen newly diagnosed patients with clinically asymmetric idiopathic PD (9 men, 9 women; mean age, 62 years; range, 47-79 years, Table 4.1.1.1.) and 16 age-matched healthy participants (8 men, 8 women; mean age, 58 years; range, 50-70 years, Table 4.1.1.1.) were included in the study. The study was approved by the local institutional ethics committee, which was the East of Scotland Research Ethics Service. Written informed consent was obtained from all participants.

Healthy subjects	Age (y)	Gender
1	60	M
2	50	F
3	50	M
4	58	F
5	65	M
6	63	F
7	58	F
8	53	M
9	56	M
10	58	F
11	64	F
12	60	F
13	53	M
14	62	F
15	70	M
16	50	M
Mean ± SD	58.12 ± 5.09	F8/M8

Patients	Age (y)	Gender	Disease duration (y)	Motor UPDRS upper limbs bradykinesia items OFF state	Motor UPDRS upper limbs bradykinesia items ON state	Treatments
1	67	F	5	8	7	LD
2	71	M	9	10	6	LD + D
3	58	M	1	14	7	D
4	68	M	3	15	9	LD + D
5	66	F	3	15	8	LD + D
6	69	M	7	15	9	L-DOPA
7	67	F	3	11	7	D
8	59	F	3	15	7	LD
9	62	M	4	15	9	LD + D
10	57	F	3	14	8	D
11	52	F	5	2	2	LD + D
12	68	F	9	15	9	D
13	47	M	1	13	9	D
14	65	M	3	10	5	LD + D
15	79	M	3	12	6	LD
16	50	M	7	14	9	LD + D
17	67	F	4	8	4	LD + D
18	61	F	3	7	1	L-DOPA
Mean ± SD	62.94 ± 8.01	F9/M9	4.22 ± 2.36	11.83 ± 3.69	6.70 ± 2.43	

Abbreviations: mo _ months; y _ years; UPDRS _ Unified Parkinson's Disease Rating Scale; SD _ standard deviation; LD_ L-DOPA; D_ Dopamine agonist

Table 4.1.1.1. *Demographic characteristics of healthy subjects and Parkinson's disease patients.*

Idiopathic PD was diagnosed according to the UK PD Society Brain Bank criteria (A. J. Hughes et al., 1992) and further confirmed by abnormal dopamine transporter SPECT in all patients. None of the patients had disabling tremor. None of the participants were on any non-PD medications that could affect the measurements performed. All participants were right-handed. The study was approved by the local institutional ethics committee. Written informed consent was obtained from all participants. Clinical disease severity was assessed with the motor section (items 3.1-3.18) of the Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale (UPDRS) (Goetz et al., 2008). The clinical assessment was performed in the ON state and practically defined OFF state in each patient. In the practically defined OFF state, patients were required to not take levodopa treatment for more than 12 hours and dopamine agonist drugs for more than 24 hours. Patients were assessed in the ON state 1 hour after taking levodopa and 2 hours after taking dopamine agonists. UPDRS scores were collected in both states.

Procedure and Experimental Design

Participants were seated in a comfortable armchair with hands relaxed on the armrest of the chair and their eyes closed. SSEPs were elicited by electrical stimulation of the median nerve at the right wrist using a constant current square-wave pulse (0.2-millisecond duration). The anode was placed over the median nerve at the wrist and the cathode 2 cm proximal to the anode. The frequency of the stimulus was 2.1 Hz, and the intensity used was the motor threshold for each subject. Electroencephalograms (EEGs) were recorded over the scalp from the left hemisphere with 3 Ag/AgCl scalp

electrodes at 3 sites on according to the International 10-20 System (F3, C3, and P3). The electrode reference was placed on the right mastoid and the ground on the left mastoid. Electrode impedance was monitored regularly during the course of the experiment and was kept less than 5 kOhms. Surface electromyography (EMG) of the right abductor pollicis brevis (AbPB) was monitored simultaneously. SSEPs were recorded in 2 conditions with randomized order in a single session. In the rest condition, the subjects were relaxed and instructed not to react to the stimulus. In the movement condition, they were instructed to make a self-paced abduction movement of the right thumb. When the EMG signal recorded from the AbPB rose above 0.15 mV, the median nerve stimulus was triggered, thus recording an SSEP at the onset of movement. For each condition, subjects made 500 thumb abductions and EEG traces were recorded for all abductions. The mean rate of thumb abductions across subjects was 0.82 Hz. Each trace lasted 470 milliseconds. During recording, the sampling rate was set at 2000 Hz, and data were online-filtered with a 20- to1000-Hz band-pass filter (CED 1401 plus, Cambridge Electronics design, Cambridge, UK), averaged, and stored in a computer for offline analysis. Artefacts exceeding 100 mV were manually rejected.

Data Analysis

Here we focused on SSEPs recorded at C3. An initial analysis determined the time of the maximal N20 and P25 components. To this end, for each subject SSEPs were averaged across all conditions, and the times of the maximal N20 and P25 components were determined. There was no significant difference in the time of occurrence of these peaks between

control subjects and patients (with mean values of 18.16 and 24.5 milliseconds for controls and 18.83 and 23.83 milliseconds for PD patients; $p>0.05$). Then for each subject and each condition I calculated the peak-to-peak amplitude of the N20-P25 component. For each, subject I then calculated the difference in this amplitude between the rest and movement onset conditions. This was the measure of sensory attenuation.

4.1.2. Results

The aim of this study was to test if PD patients showed a reduced SA compared to age-matched healthy controls.

As expected, healthy participants showed attenuation of the N20-P25 component at movement onset ($p < 0.05$; $t_{15} = 3.67$, Fig. 4.1.2.1. A, D). PD patients OFF medication showed no sensory attenuation at movement onset ($p = 0.37$; $t_{17} = 0.92$; Fig. 4.1.2.1. B, D), whereas they did show attenuation of the N20-P25 component when ON medication ($p < 0.05$; $t_{17} = 2.70$). Furthermore, the difference in N20-P25 attenuation was reduced in PD patients OFF compared with ON medication ($p < 0.05$; $t_{17} = - 2.21$; Fig. 4.1.2.1. C, D).

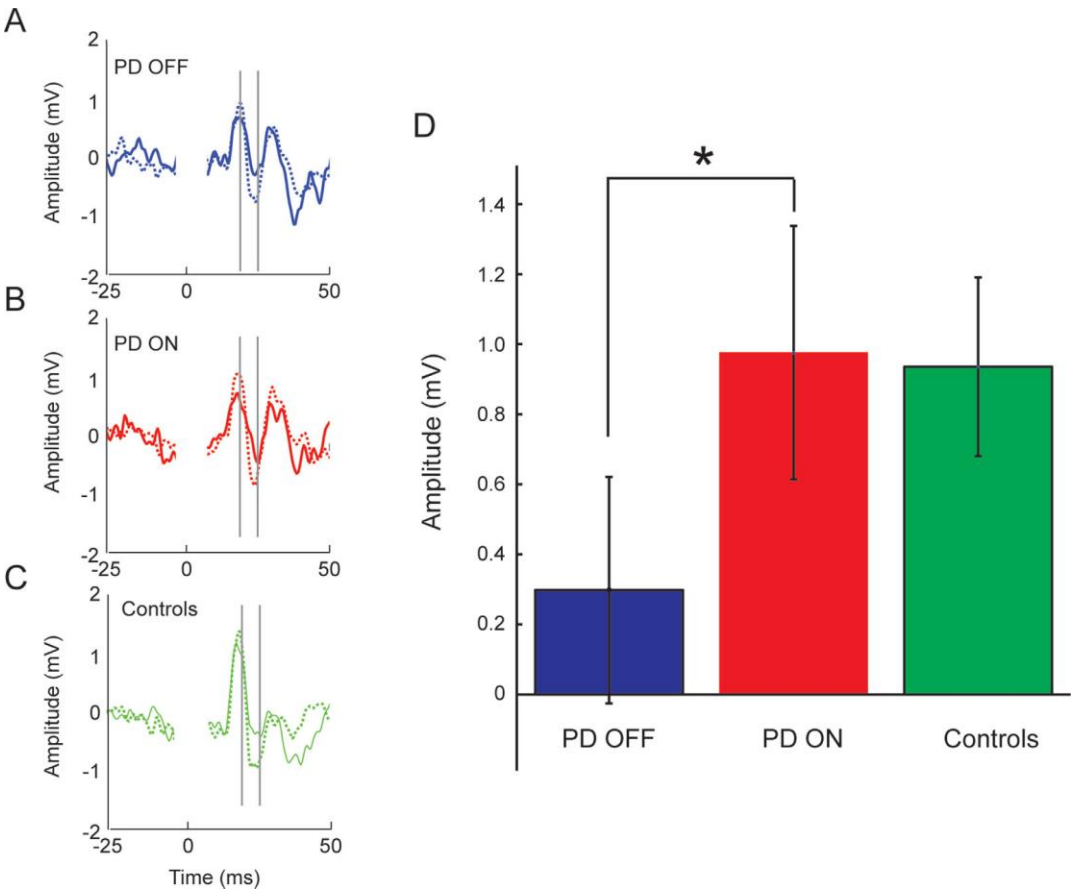


Figure. 4.1.2.1. *A-C) Average SSEPs across participants recorded from C3 for PD patients OFF medication (A), ON medication (B), and control subjects (C). Solid lines show data for median nerve stimulation given at movement onset and dotted lines during baseline. The gray lines show the mean time of the peaks of the N20 and P25 components. (D) Mean amplitude of the N20-P25 component averaged across participants for the for PD patients OFF medication (blue), ON medication (red), and control subjects (green). Error bars show standard error of the means. *Significant within subject difference of medication for the PD participants.*

Having shown that SA was modulated by dopaminergic treatment and that SA was significantly attenuated in PD patients OFF medication, I next tested whether the severity of patient motor symptoms measured through the UPDRS scores was related to the degree of SA. Although qualitatively there appeared to be a negative relationship between the individual patients' UPDRS scores and the degree of sensory attenuation both ON and OFF medication (Fig. 4.1.2.2., filled and open circles, respectively), these were not statistically significant (R^2 = 0.02, p = 0.54 OFF medication and R^2 = 0.05, p = 0.35 ON medication).

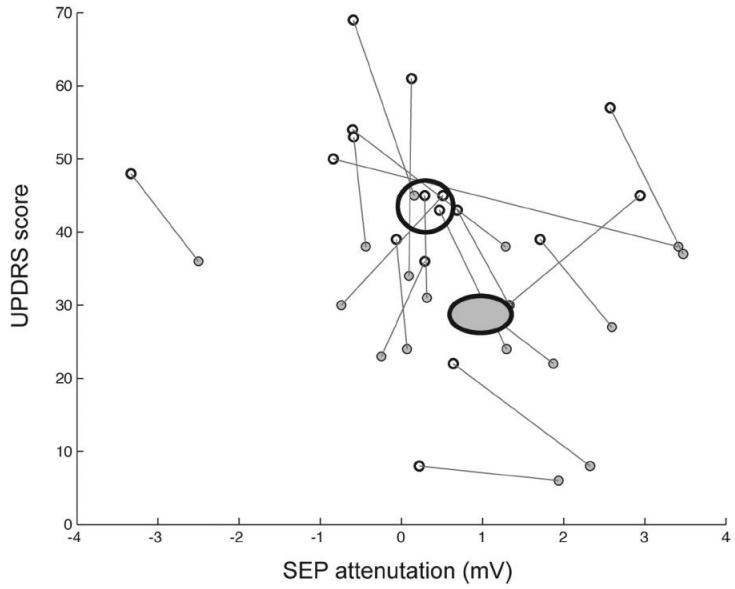


Figure. 4.1.2.2. *The relationship between the SSEP attenuation effect (baseline movement) and the patients' UPDRS scores both OFF (open circles) and ON (filled circles) medication. The data for the same subject are joined with the gray line. As is clear, the majority of patients' data move in the direction of high UPDRS, low SSEP attenuation OFF medication to low UPDRS and high SSEP attenuation ON medication. The larger ellipses are centered on the mean value of the sensory attenuation and UPDRS score for OFF (open) and ON (filled) medication. The size of the ellipse shows the SSEP in these 2 dimensions.*

4.1.3. Discussion

The aim of this study was to test if patients diagnosed with PD showed a reduction of SA, which was hypothesized as the neurophysiological mechanism underlying the bradykinesia. Here I present data that show that at movement onset PD patients off medication do not have significant sensory attenuation; however, when they receive medication that improves their motor function, sensory attenuation occurs. This result might appear to be at odds with previous studies that have shown normal sensory attenuation in PD (Cheron, Piette, Thiriaux, Jacquy, & Godaux, 1994; Insola et al., 2004). However, this most likely reflects critical differences in the task design. In Cheron et et al. (Cheron et al., 1994) and Insola et al. (Insola et al., 2004) patients were instructed to make vigorous wrist flexion and extension movements, and SSEPs were recorded during periods of continuous movement. Here, we asked subjects to make a movement of the thumb and timed the median nerve stimuli to be delivered at the onset of movement. This difference is fundamental, as the theoretical prediction from active inference is that movement in PD will be associated with a decrease in sensory attenuation at movement onset. We did not identify a significant correlation between the change in sensory attenuation that occurred following medication intake in patients with PD and the change in a clinical measure of motor performance. One reason for this could be the sensitivity of the UPDRS in assessing change in bradykinesia. The UPDRS is not a parametric variable. The score is limited to integer values within a certain range. It is the nonparametric nature of the measure that potentially makes this measure have statistically low sensitivity in the correlation analysis. In

addition, there are many different aspects to bradykinesia, and here the UPDRS score is an aggregate score of these aspects.

In conclusion, bradykinesia lacks a clear pathophysiological framework, although it is a cardinal clinical feature of PD. The results presented here are consistent with the prediction of the active inference framework and are in support of the hypothesis that a failure in sensory attenuation prior to movement onset contributes to the difficulties in movement initiation in PD. More specifically is that a pathology in modulating the gain of the afferent signal in PD patients underlies some clinical aspects of bradykinesia. In light of these results, I was interested in my next study to collect parametric measures of the different aspects of bradykinesia to more sensitively test whether the failure in SSEP attenuation is indeed related to some of the cardinal bradykinetic aspects of PD. My next study was performed in large groups of subjects to understand how SA may link to other pathological abnormalities seen in PD at the onset of movement, for example, beta band desynchronization.

Chapter 5 – DOPAMINERGIC MODULATION OF SENSORY ATTENUATION IN PARKINSON'S DISEASE. IS THERE AN UNDERLYING MODULATION OF BETA POWER?

5.1. Sensory attenuation at the onset of movements and beta oscillations

In the previous chapter I showed that SA prior to and during movement (as measured by a decrease in the amplitude of N20-P25 component of SSEPs elicited by median nerve stimulation) is significantly reduced in patients with PD OFF medication and this is normalized by dopaminergic medication. Whereas, as expected, healthy participants showed attenuation of the N20-P25 component at movement onset. The first aim of this study was to replicate the results of the previous chapter in a completely naïve group of PD patients. The prediction was an interaction in the SSEPs amplitude between group and time with the SSEP being more greatly attenuated in healthy controls at the onset of active movement than the patient groups in OFF state. Furthermore, it was predicted that there would not be any significant differences SA between healthy participants and patients ON medication. A second aim here was to test whether SSEPs attenuation was modulated as a function of disease and voluntary movement. In other words, if there was a correlation between the difference in SSEP N20-P25 amplitude between baseline and movement conditions with measurements of bradykinesia in the tested hand using appropriate items from the UPDRS and quantification of slowing and decrement in repetitive movement using parametric measures of the tapping. The prediction was that SSEP attenuation would correlate with movement such that the faster and more

vigorous movements would be positively correlated with the degree of the SA. I predicted that across subjects the lower (better) the UPDRS scores and the less slowing and decrement in amplitude of tapping, the greater the SA measured at movement onset. If this is the case, these results would be another support of the pathophysiological role of SA in the contest of bradykinesia.

The active inference theory makes more detailed predictions. It predicts that SA will be driven by a change in the precision of the sensory expectation, with lower precision leading to greater SSEP attenuation.

The aim of the second part of the study described in this chapter was to test the hypothesis that these modulations in SA would be correlated with modulation in beta power in the sensorimotor cortex. It is well known that beta oscillations over sensorimotor cortex decrease prior to and during movement (Pfurtscheller & Lopes da Silva, 1999).

Tan et al. (Tan, Wade, & Brown, 2016) tested a novel theory of the functional role of sensorimotor PMBS that provides an important link between theoretical models of motor control related with a phenomenon called uncertainty and neurophysiological measures of sensorimotor activity. Indeed, voluntary movements stimulate peripheral sensory receptors that provide sensory feedback of the motor act. In the active inference model in which an active movement lead to predict the sensory consequences of that movement (through forward models) and, consequentially, lead to compare this prediction to the actual sensory input. Any difference between the predicted and actual sensory input will result in a prediction error, which is used to update the forward model for more

accurate future predictions. To determine the relevance of any prediction errors, the model requires estimations of both the uncertainty in the motor prediction and the uncertainty of the actual sensory input (Kording & Wolpert, 2004). Tan et al. (Tan et al., 2016) manipulated task uncertainty to modulate the uncertainty in parameters of the model and tested the hypothesis that PMBS was correlated with these parameters. In other words, these authors predicted that PMBS would correlate with this uncertainty rather than with the movement error. The authors reported that the amplitude of the PMBS over sensorimotor cortex was negatively correlated with this uncertainty variable. This result is consistent with a novel functional role of PMBS, which suggests that beta oscillations are related to the uncertainty of the parameters of generative models that underlie motor control. In other words, sensorimotor beta oscillatory power might be either the neurophysiological correlate of the estimate of uncertainty or causally modulating the uncertainty. Palmer C et al. (C. Palmer et al., 2016) highlighted that this potential correlation between PMBS and sensory uncertainty might implicate that beta oscillatory activity is a promising candidate for this gating mechanism. This finding is particularly relevant for the application of this theoretical account to explain akinesia and bradykinesia. In people with PD, beta oscillations in the motor network and in the STN are higher during rest and have been causally implicated in movement impairment rather than being just an epiphenomenon of the diseased state (Little & Brown, 2014).

One theory therefore is that patients with PD have high sensory precision such that when they decide to move they cannot attenuate this precision enough to allow the influence of top-down proprioceptive predictions to

supersede. This theory is supported by the results of the study, described in the previous chapter which has demonstrated decreased SA in patients diagnosed with PD compared to age-matched healthy control. Therefore, here it was tested if the specific time course of the SA (it is greater in healthy controls than in patients and greater in patients ON medication than those OFF medication at the onset of the movement) is correlated with modulations in beta power during movement execution. The prediction was that modulations in beta power will be positively correlated with the time course of SSEPs modulation. If this is the case, it will establish a statistical dependency between beta power and sensory attenuation.

5.1.1. Methods

Sixteen diagnosed patients with clinically asymmetric idiopathic PD (10 men, 6 women; mean age, 68 years; range, 52-79 years; Table 5.1.1.1) and 22 age and sex matched healthy participants (14 men, 8 women; mean age, 67 years; range, 50-80 years) were included in the study. Idiopathic PD was diagnosed according to the UK PD Society Brain Bank criteria (A. J. Hughes et al., 1992) and further confirmed by abnormal dopamine transporter SPECT in all patients. None of the patients had disabling tremor. None of the participants were on any non-PD medications that could affect the measurements. All participants were right-handed. The study was approved by the local institutional ethics committee, which was the East of Scotland Research Ethics Service. Written informed consent was obtained from all participants. Clinical disease severity was assessed with the motor section (items 3.1-3.18) of the UPDRS (Goetz et al., 2008).

The clinical assessment was performed in the ON state and practically defined OFF state in each patient.

Furthermore, the amplitude and the frequency of a minute right hand tapping test with the Cyber Glove was recorded in both pharmacological states.

To reach the OFF state, patients were required not to take levodopa for at least 12 hours and dopamine agonists for at least 24 hours prior to testing. Patients were assessed in the ON state 1 hour after taking levodopa or 2 hours after taking dopamine agonists. UPDRS scores were collected in both states (Table 5.1.1.1.).

	Age (y)	Gender	Disease duration (y)	Motor UPDRS upper limbs bradykinesia items OFF state	Motor UPDRS upper limbs bradykinesia items ON state	Treatments
1	72	M	11	11	6	L
2	75	F	4	9	5	L
3	61	M	2	6	3	L
4	75	M	5	11	5	L
5	77	F	10	9	5	L
6	68	F	4	6	3	L
7	56	M	4	8	3	L
8	70	F	6	6	3	L+D
9	69	M	6	9	4	L+D
10	79	F	12	10	6	L+D
11	68	F	10	12	6	L+D
12	52	M	10	12	6	L+D
13	62	M	3	8	3	L+D
14	68	M	8	12	9	L+D
15	72	M	5	8	3	L+D
16	68	M	5	8	3	L+D
Mean $\pm$ SD	68.1 $\pm$ 6.9	F8/M12	6.5 $\pm$ 2.9	9 $\pm$ 2	4.3 $\pm$ 1.7	

Table 5.1.1.1. *Clinical and demographic characteristics of patients with Parkinson disease (Mo _ months; y _ years; UPDRS _ Unified Parkinson's Disease Rating Scale; SD _ standard deviation; L_ L-DOPA; D_ Dopamine agonist).*

Procedure and experimental design

Participants were seated in a comfortable armchair with hands relaxed on the armrest of the chair and their eyes closed. Two electrodes were placed on the surface of the skin in the center of the wrist above the median nerve with the cathode more distal just below the crease of the wrist. SSEPs were elicited by electrical stimulation of the median nerve at the right wrist using a constant current square-wave pulse (0.2 ms duration). The anode was placed over the median nerve at the wrist and the cathode 2 cm proximal to the anode. The frequency of the stimulus was 0.5 Hz. The intensity of the stimulation at threshold (slight thumb twitch) was identified and then increased by 1 mA to produce a definite thumb twitch. The intensity remained the same throughout the experiment.

Electrical activity was recorded at the scalp using a 128 channels Biosemi ActiveTwo AD-box EEG. EEG was recorded at a sampling rate of 2048 Hz.

Surface electromyography (EMG) of the right abductor pollicis brevis (APB) was monitored simultaneously.

SSEPs were recorded in three conditions in a single session.

In the baseline condition, the subjects were relaxed and instructed not to react to the stimulus. The frequency of the median nerve stimulation was 0.5 Hz and the applied intensity was the motor threshold for each subject. Subjects received 500 stimulations in this condition.

In the movement condition, subjects were instructed to make a self-paced abduction movement of the right thumb with a frequency of around a movement every second. At the onset of the movement, the median nerve

stimulus was automatically triggered. The frequency of movements was recorded. The applied intensity was the motor threshold for each subject. Participants made 500 thumb abductions.

In the rest condition, the subjects were relaxed and instructed not to react to the stimulus. In distinction to the baseline condition here the median nerve stimulations were given at precisely the same times as the self-paced movements in the movement condition and these times were taken from the times of the stimulations from the movement conditions. The applied intensity was the motor threshold for each subject.

Data Analysis

Measure of SSEPs components and sensory attenuation

EEG data analyses were performed in MATLAB 2013b (Math Works, Natick, MA, USA), using the software Statistical Parametric Mapping (SPM12, Wellcome Department of Imaging Neuroscience, London, UK).

The SSEPs produced at movement onset has previously been employed to assess the degree of SA during active movement as the SSEP elicited by stimulation at this time point it is not confounded by any possible effect of the afferent signal produced by the movement. The initial analysis was focused on modulations in the SSEP components, specifically the amplitude of the N20 and P25, as a function of group, PD patients ON and OFF medication and healthy controls. The analysis focused on the peak-to-peak amplitude of the N20-P25 component for each subject SSEPs. The EEG data were analysed in SPM12.

Offline the data were high-passed filtered at 0.1 Hz. The data were epoched to the time of the onset of the median nerve stimulation taking the 100 ms before stimulation and 250 ms after the stimulation. The data were baseline corrected by subtracting the average of the signal in a window from 20 ms to 5 ms prior to median nerve stimulation. This function corrected the data by subtracting from each channel the mean from 20ms to 5ms relative to the stimulus onset.

Artefacts exceeding 100 mV were manually rejected.

SSEPs were averaged across the 500 trials of each condition. The baseline condition was the reference to select the appropriate channels to see N20 and P25. Using the scalp map function of SPM 12, the ROI (region of interest) over sensorimotor cortices were selected based on electrodes that showed a negative peak at around 20 ms and a positive peak around 25–35 ms after the stimulus.

Then, the data from the selected channels were averaged and the amplitude and the time data point of N20 as well as P25 were measured. Subsequently, the amplitude of N20 and P25 in the rest condition data as well as movement condition data at the same correspondent data points that it was found in the baseline condition. This analysis aimed to avoid bias in the measurement related with the experimental condition.

The difference in the absolute amplitude of the peak N20-P25 between the rest and movement onset conditions was calculated. This was the measure of sensory attenuation

Analysis of parametric measures of tapping and quantification of bradykinesia through EMG data

The fingers-tapping performed using the cyber glove was recorded through a Matlab script. The data were then analysed in Matlab; the amplitude and the frequency of each tapping movement in a minute of interval time were calculated using Welch's power spectral density estimate of the time series of the tapping as recorded by the CyberGlove. The data were then averaged, and the peak amplitude and frequency at the peak amplitude of the tapping was taken for each pharmacological state of each patient. These were the parametric measures of tapping.

The regression analysis between SA and parametric measures was performed to test the hypothesis of a correlation between dopaminergic modulation of SA and dopaminergic improvement of bradykinesia.

Analysis of beta power in movement and rest condition

Offline the EEG data from the rest condition were analysed in SPM12 and modulations in power in different frequencies were studied as a function of time relative to the time of the thumb abduction. Given the results of previous studies, it was predicted that in healthy subjects power in beta oscillations will be attenuated prior to the thumb movement and will be augmented once the movement has ended (Pfurtscheller & Lopes da Silva, 1999).

After raw data conversion, EEG data were re-referenced by deducting the average signal from two external electrodes attached to the subjects' earlobes from the signal from each EEG electrode.

High pass (0.1 Hz) filter was applied and the signal was down-sampled to 400 Hz.

A trigger was sent to the EEG system at the time of every median nerve stimulus. The data were epoched to the time of the onset of movement, which triggered the median nerve stimulation, taking the 1000 ms before the onset and 1000 ms after.

The EEG recording contained the eye movements/blinks and I did not remove them from the data during the epoch process. I am aware that the eye blinks interfere with the beta oscillations. Indeed, reduced blink reduced beta desynchronization in OFF state in PD and increased blink in ON state. Therefore, this was an additional confound.

The different experimental blocks were merged into a single file.

For the time–frequency analysis, the power of the EEG signal at each frequency from 1 to 99 Hz in steps of 2 was estimated using the Morlet spectral estimation in SPM. The data were rescaled using a logarithmic transformation and averaged across all trials.

A time–frequency analysis was conducted to investigate whether there was any aspect of the oscillatory neural signal that correlated significantly with the SA.

The time–frequency data files were converted into images for statistical analysis in SPM.

The time–frequency data were averaged over electrode channels selected for the SSEP analysis on the scalp map to investigate the modulation of

beta power in each condition (rest and movement) for each subject and in each pharmacological state for each patient.

Subsequently, the time-frequency images for the rest condition for each subject were averaged across all subjects and 3 times windows corresponding to the three phases of beta oscillations modulation with median nerve stimulation were calculated: back ground (between 180 and 625 ms before the stimulus), suppression (between 165 and 378 ms after stimulus) and rebound (between 535 and 980 ms). These windows were defined from the modulation of the beta power in the rest condition.

The beta power obtained by averaging over the frequency of 15-25 Hz was then averaged over each selected time window across subjects of each group to have a value of beta power for each time window per group per condition. Subsequently, we obtained a value of beta power modulation for each group and each time window through a subtraction of beta power value between rest and movement condition.

The value of beta power modulation was then regressed against the amplitude of SA per group per time window.

Finally, we performed a regression analysis between the amplitude of beta power and amplitude of SSEPs for each group per time window per condition.

5.1.2. Results

SSEPs components and sensory attenuation

The averaged SSEPs over our ROI (channels over the somatosensory cortex) across participants for PD patients OFF medication (1A), ON medication (1B), and control subjects (1C) are shown in Figure 5.1.2.1.

Repeated measures ANOVA with the group (ON vs OFF) and condition (rest vs movement) as factors showed a significant effect of the condition ($p< 0.05$; $F (1, 30) = 39.46$; $Eta^2 = 0.537$) and a significant interaction between condition and pharmacological state ($p < 0.05$; $F (1, 30) = 6.33$; $Eta^2 = 0.157$). Post-hoc pairwise comparisons revealed a significant difference between N20-P25 peak to peak amplitude at rest condition and movement condition ($p < 0.05$; $t (30) = 5.85$).

As expected, healthy participants showed attenuation of the N20-P25 amplitude at movement onset (2.13 ± 1.87) compared to rest condition (4.8 ± 2.84) ($P < 0.05$; $t (21) = 7.45$, Fig. 5.1.2.2.a).

PD patients OFF medication showed mild attenuation of the N20-P25 component at movement onset (3.99 ± 2.31) compared to rest condition (5.03 ± 3.29) ($P < 0.05$; $t (15) = 2.52$; Fig. 5.1.2.2 b), and they showed greater attenuation of the N20-P25 component at the onset of movement (2.59 ± 1.79) compared to the rest condition (5.02 ± 2.94) when ON medication ($P < 0.05$; $t (15) = 5.95$; Fig. 5.1.2.2. c).

Of note, there was a significant difference in the amplitude of N20-P25 peak during the movement condition between OFF state (3.99 ± 2.31) and ON

state (2.59 ± 1.79) ($p = < 0.05$; $t (15) = 3.32$) with a smaller amplitude in the ON state.

There was no difference in the N20-P25 amplitude during the rest condition between OFF state (5.03 ± 3.29) and ON state (5.02 ± 2.94) ($p =>0.05$; $t (15) = 0.017$).

The sensory attenuation (defined as difference in the amplitude of N20-P25 peak between rest condition and movement condition) revealed a significant difference between OFF (1.29 ± 1.55) and ON state (2.42 ± 1.55) in PD patients ($p = < 0.05$; $t (15) = -3.28$) with greater sensory attenuation in ON state.

There was no difference in the sensory attenuation between PD patients in ON state (2.42 ± 1.55) and healthy subjects (2.74 ± 1.61) ($p = >0.05$, $t (36) = -0.46$).

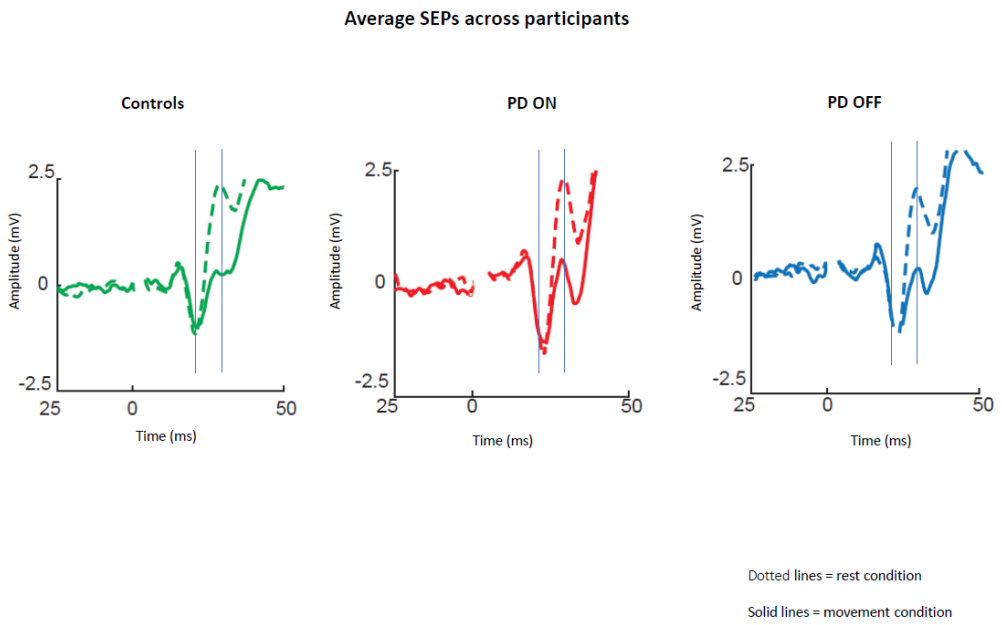


Figure 5.1.2.1. *Average SSEPs across participants recorded from the left somatosensory cortex for PD patients OFF medication (A), ON medication (B), and control subjects (C). Solid lines show data for median nerve stimulation given at movement onset and dotted lines during baseline. The gray lines show the mean time of the peaks of the N20 and P25 components.*

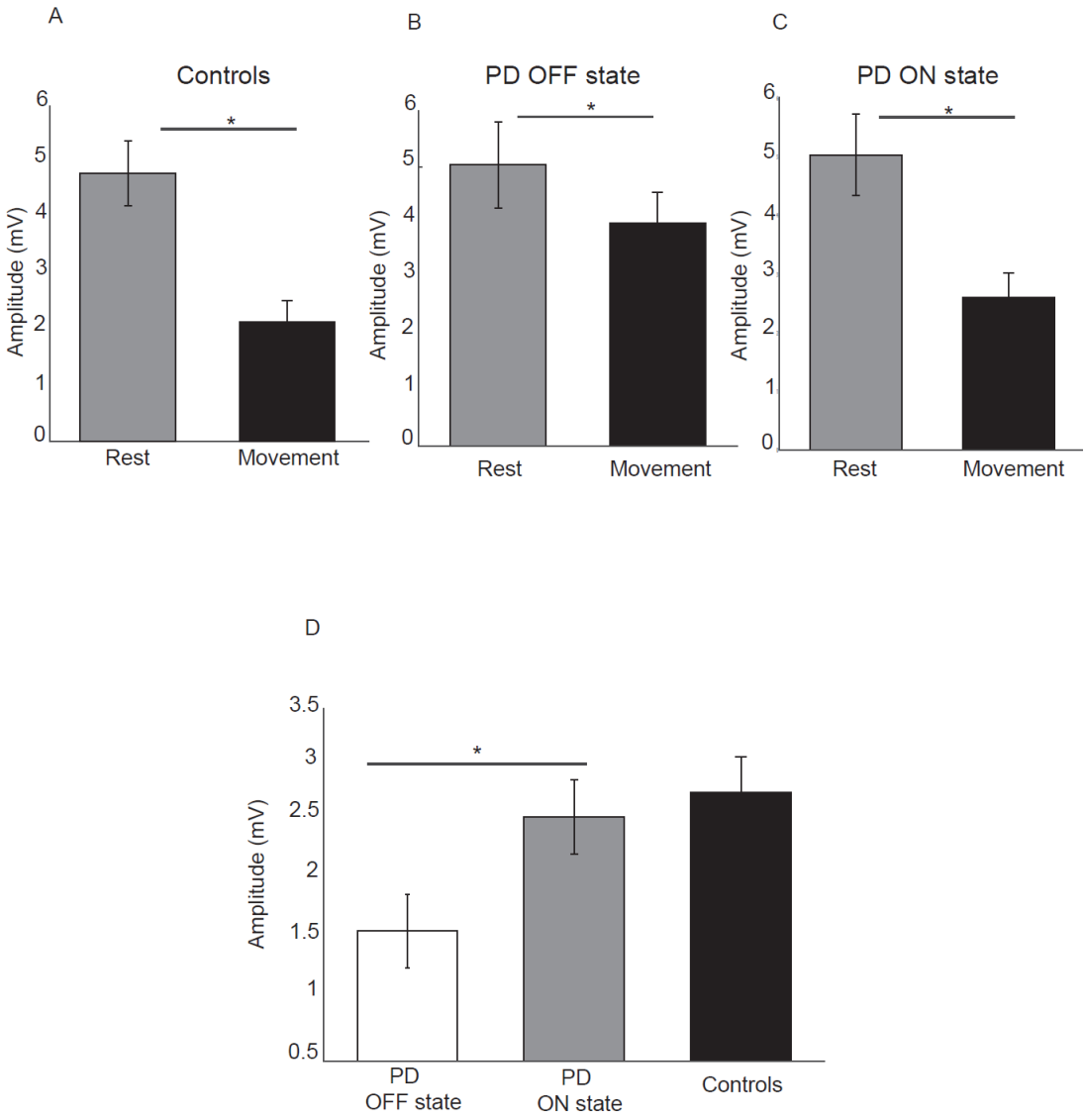


Figure 5.1.2.2. *Mean amplitude of the N20-P25 component for each condition for control subjects (A), PD patients OFF medication (B), ON medication (C). Error bars show standard error of the means. Mean difference of the N20-P25 amplitude between rest condition and movement condition in PD patients OFF medication, ON medication and controls (D).*

Having shown that SA was modulated by dopaminergic treatment and that SA was significantly attenuated in PD patients ON medication, I next tested whether the severity of right arm bradykinesia measured through the UPDRS scores and the cybernetic glove was related to the degree of SA. There was no statistically significant correlation between SA and UPDRS scores (R^2 = 0.001, p = 0.893 OFF medication (Figure 5.1.2.3 A) and R^2 = 0.001, p = 0.924 ON medication (Figure 5.1.2.4. A) as well as between SA and frequency of the fingers tapping (R^2 = 0.059, p = 0.330 OFF medication (Figure 5.1.2.3. B) and R^2 = 0.002, p = 0.867 ON medication (Figure 5.1.2.4. B) or amplitude of the fingers tapping (R^2 = 0.06, p = 0.323 OFF medication (Figure 5.1.2.3. C) and R^2 = 0.008, p = 0.718 ON medication (Figure 5.1.2.4. C).

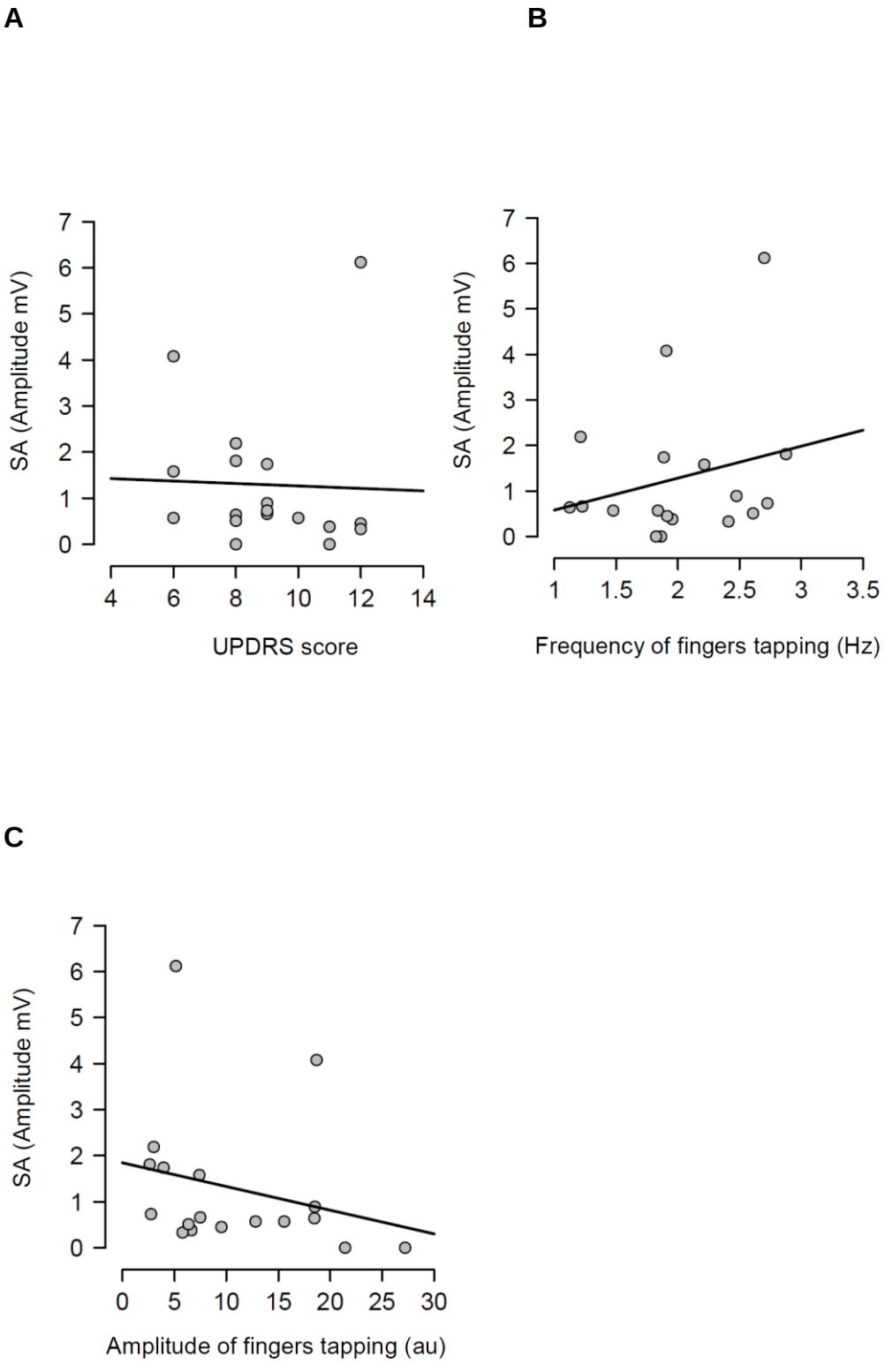


Figure 5.1.2.3*. Figures relate to the regression analysis in PD OFF between SA and each measures of bradykinesia.*

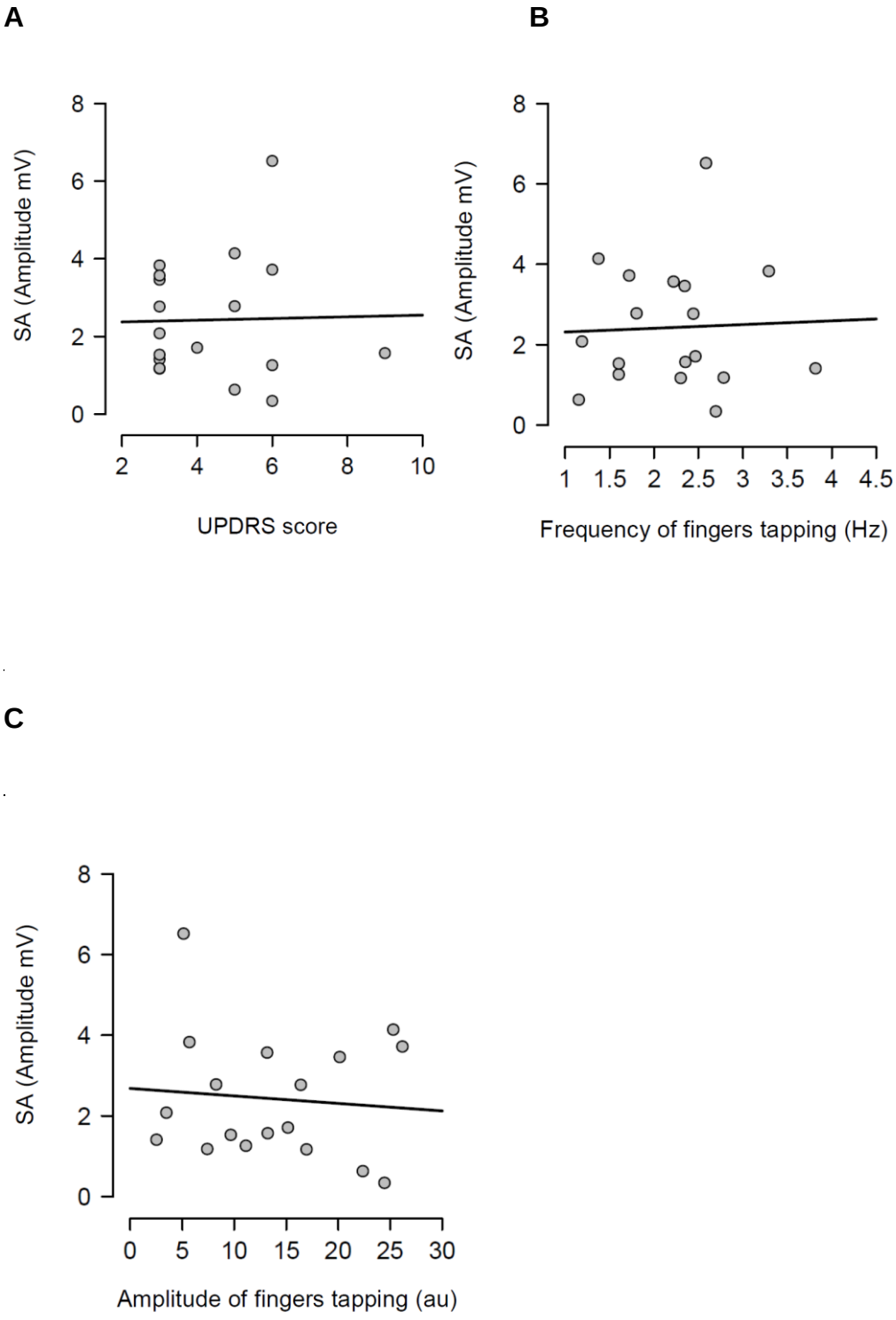


Figure 5.1.2.4*. Figures relate to the regression analysis in PD ON between SA and each measures of bradykinesia.*

After having tested the hypothesis of a potential correlation between SA and each measure of bradykinesia in the individual pharmacological state. I was interested to test if there was a potential correlation between the dopaminergic modulation of SA and the dopaminergic modulation of each measure of bradykinesia. In other words, I tested a correlation between the changes of SA between OFF and ON states and the changes of each measure of bradykinesia between OFF and ON states.

There was not statistically significant correlation between dopaminergic modulation of SA and changes of UPDRS scores (R^2 0.016, $p = 0.616$) (Figure 5.1.2.5 A). Interestingly, the was a significant correlation between dopaminergic modulation of SA and changes of frequency of the fingers tapping ($R^2 = 0.623$, $p < 0.001$) (Figure 5.1.2.5 B) or amplitude of the fingers tapping ($R^2 = 0.021$, $p = 0.562$) (Figure 5.1.2.5 C).

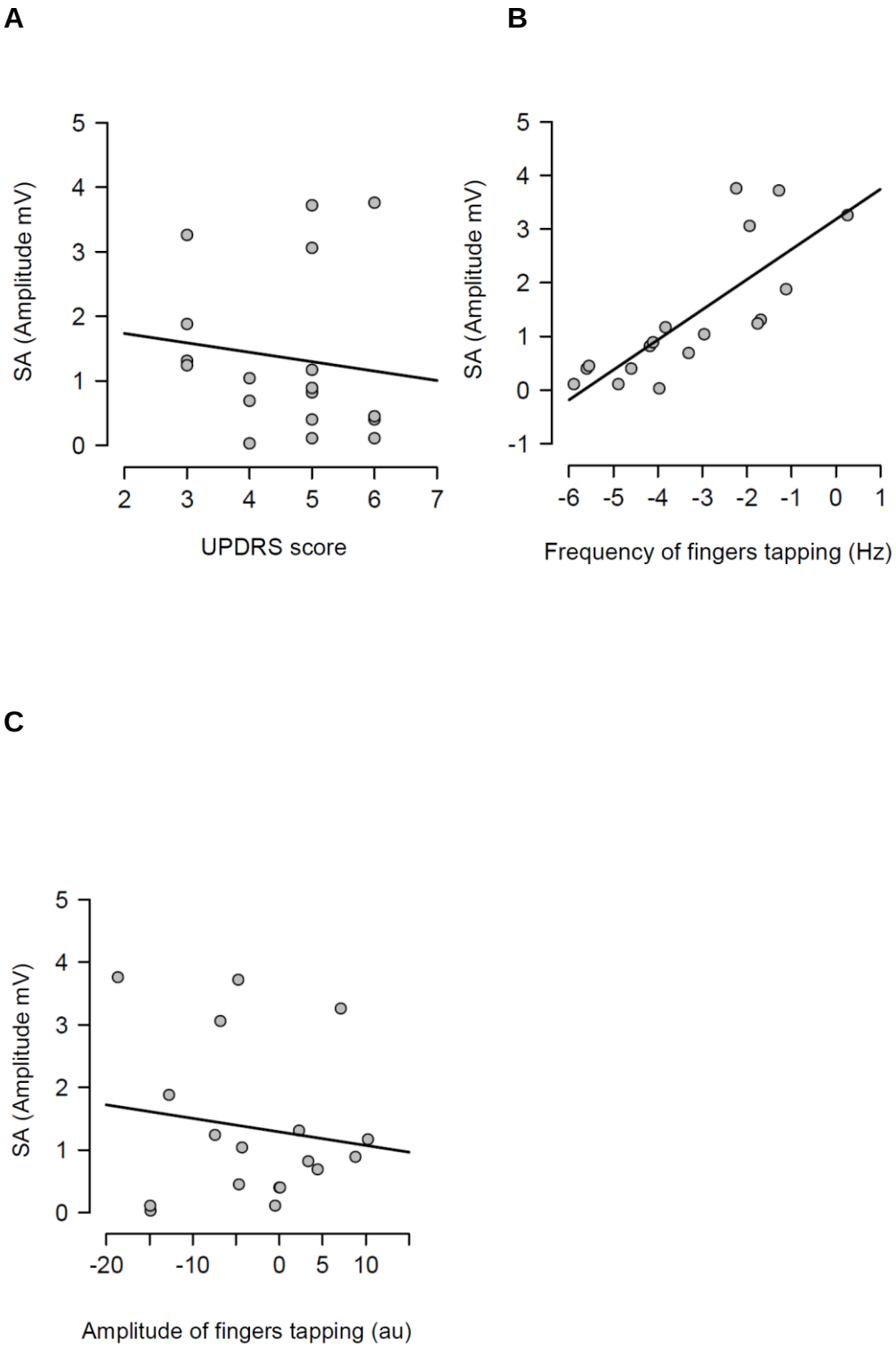


***Figure 5.1.2.5**. Figures relate to the regression analysis between dopaminergic modulation of SA and dopaminergic changes of each measure of bradykinesia. The dopaminergic modulation was calculated through the difference between OFF and ON values for each variable.*

Beta oscillations modulation

Having demonstrated that there was a modulation of SSEPs over condition, the second aim was to test if the SA, which was greater in healthy controls than in patients and greater in patients ON medication than those OFF medication at the onset of the movement, was correlated with modulations in beta power over sensorimotor cortex during movement execution.

Firstly, I tested the hypothesis that the 2 groups (healthy controls and PD patients) showed a modulation of beta power as function of time in each experimental condition. The prediction was to find power in beta oscillations attenuated prior to the thumb movement and a rebound at the end of the movement as it has been showed in the literature by several studies. After averaging the time-frequency images across subjects for each group, the changes of the beta power spectrum (interval of frequency at 15-30 Hz) as function of time in each condition were evident. Indeed, beta power was clearly evident prior to movement in the baseline period, suppressed in the motor preparation and execution period and, finally, rebounded at the end of the thumb movement.

The modulation of beta oscillations in the rest condition averaged across subjects for each group is showed in the figure 5.1.2.6.

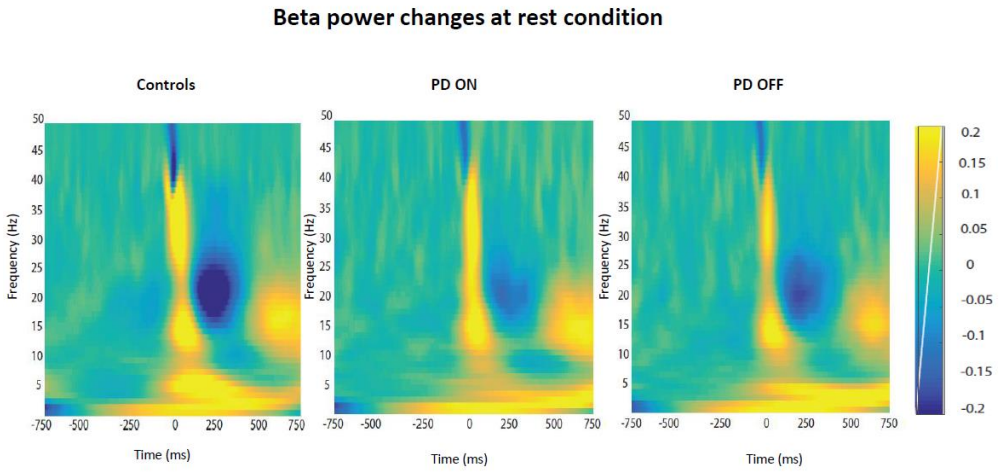


Figure 5.1.2.6. *Modulation of power spectrum as function of time in the rest condition*

Following the qualitative analysis, a quantitative analysis of the beta oscillations was performed in three timing windows selected as explained in the methods section. There were selected 3 times windows corresponding to the three phases of beta oscillations modulation calculated as background (between 180 and 625 ms before the stimulus), suppression (between 165 and 378 ms after stimulus) and rebound (between 535 and 980 ms).

The quantitative analysis confirmed that the amplitude of beta oscillations was different as function of time. Indeed, beta oscillations amplitude showed a significant statistical difference in each group and in each condition over the 3 different timing windows (Figure 5.1.2.7).

Repeated measures 2 x 2 x 3 ANOVA with the group (healthy controls vs patients (ON)), condition (rest vs movement) and phase (background, suppression and rebound) as factors did not show an effect of the group ($p>0.05$; $F(1,36) = 0.040$; $Eta^2 = 0.001$). It showed a significant effect of the condition ($p< 0.05$; $F(1, 36) = 34.88$; $Eta^2 = 0.493$) and a significant interaction between condition and group ($p< 0.05$; $F(1, 36) = 8.739$; $Eta^2 = 0.195$). There was a significant effect of the phase ($p< 0.05$; $F(1, 36) = 91.185$; $Eta^2 = 0.717$). There was not a significant interaction between phase and group ($p> 0.05$; $F(1, 36) = 2.834$; $Eta^2 = 0.073$). There was a significant interaction between condition and phase ($p< 0.05$; $F(1, 36) = 15.047$; $Eta^2 = 0.295$).

Post-hoc pairwise comparisons with Bonferroni corrections did not reveal significant difference between the two groups (healthy participants vs PD ON state) in the rest condition in each phase: background ($p > 0.05$, $t(36)$

= 1.090), suppression (p> 0.05, t (36) = 0.491) and rebound (p>0.05, t (36) = 1.235). The two groups did not show significant difference neither in the movement condition in each phase: background (p > 0.05, t (36) = -0.645), suppression (p> 0.05, t (36) = -0.579) and rebound (p>0.05, t (36) = -0.370).

Furthermore, post-hoc pairwise comparisons showed significant differences between the rest and movement condition in the background phase (p < 0.05, t(37) = -5.356), suppression (p<0.05, t(37) = -4.156) and rebound (p<0.05, t(37) = -6.795) over the two groups.

Repeated measures 2 x 2 x 3 ANOVA with the group (healthy controls vs patients (OFF)), condition (rest vs movement) and phase (background, suppression and rebound) as factors did not show an effect of the group (p>0.05; F (1,36) = 0.0765; Eta^2 = 0.021). It showed a significant effect of the condition (p< 0.05; F (1, 36) = 58.04; Eta^2 = 0.617) and a significant interaction between condition and group (p< 0.05; F (1, 36) = 7.931; Eta^2 = 0.181). There was a significant effect of the phase (p< 0.05; F (1, 36) = 98.454; Eta^2 = 0.732). There was not a significant interaction between phase and group (p> 0.05; F (1, 36) = 2.366; Eta^2 = 0.062). There was a significant interaction between condition and phase (p< 0.05; F (1, 36) = 20.392; Eta^2 = 0.362).

Post-hoc pairwise comparisons with Bonferroni corrections did not reveal significant difference between the two groups (healthy participants vs PD OFF state) in the rest condition in each phase: background (p > 0.05, t (36) = 1.446), suppression (p> 0.05, t (36) = 1.125) and rebound (p>0.05, t (36) = 1.725). The two groups did not show significant difference neither in the

movement condition in each phase: background ($p > 0.05$, $t(36) = 0.112$), suppression ($p > 0.05$, $t(36) = 0.217$) and rebound ($p > 0.05$, $t(36) = 0.484$).

Furthermore, post-hoc pairwise comparisons showed significant differences between the rest and movement condition in the background phase ($p < 0.05$, $t(37) = -6.739$), suppression ($p < 0.05$, $t(37) = -5.002$) and rebound ($p < 0.05$, $t(37) = -8.876$) over the two groups.

Mean amplitude of the beta oscillations for each condition for each group

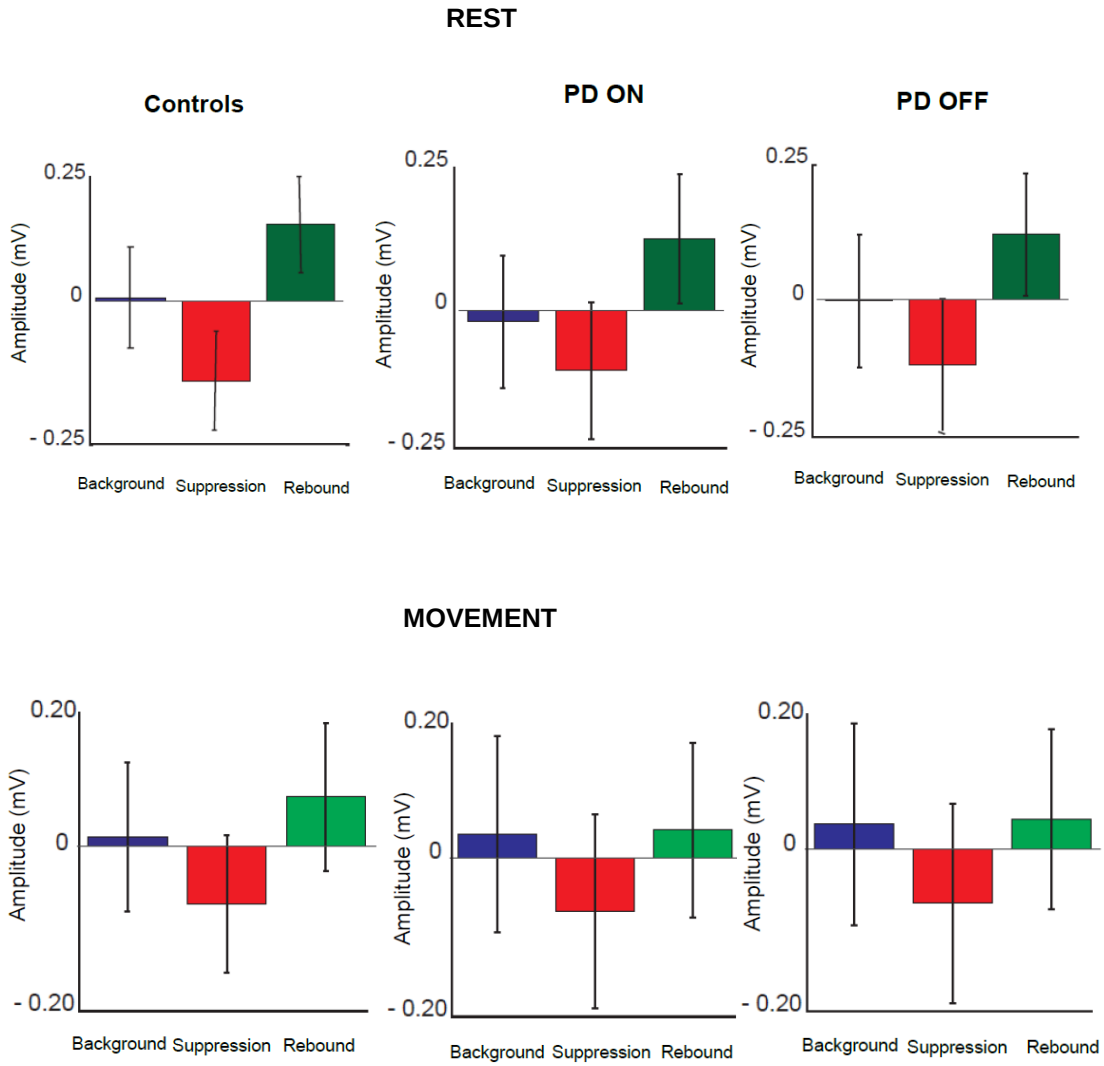


Figure 5.1.2.7. *Quantitative analysis of beta oscillations amplitude for each condition and each group in the selected time windows.*

Having found a modulation of beta oscillations amplitude as function of time, the subsequent aim was to test if there was a correlation between beta oscillations amplitude changes across the two conditions and SSEPs changes across the two conditions, which was the measure of SA.

This correlation analysis was performed separately for each time window in each group of participants.

There was no evidence that SA and beta oscillations amplitude modulation were correlated. Indeed, healthy participants did not show a significant correlation between beta oscillations amplitude modulation and SA in background phase (R^2 = 0.04, p=0.51), suppression phase (R^2 = 0.08, p=0.24) or the rebound phase (R^2 = 0.06, p=0.37). The absence of a correlation between these two neurophysiological phenomena was evident also in the PD patients group in ON (background phase, R^2 = 0.11, p=0.56; suppression phase, R^2 = 0.07, p=0.73; rebound phase, R^2 = 0.14, p=0.43) as well as in OFF state (background phase, R^2 = 0.005, p=0.41; suppression phase, R^2 = 0.003, p=0.31; rebound phase, R^2 = 0.006, p=0.15). (Figure 5.1.2.8).

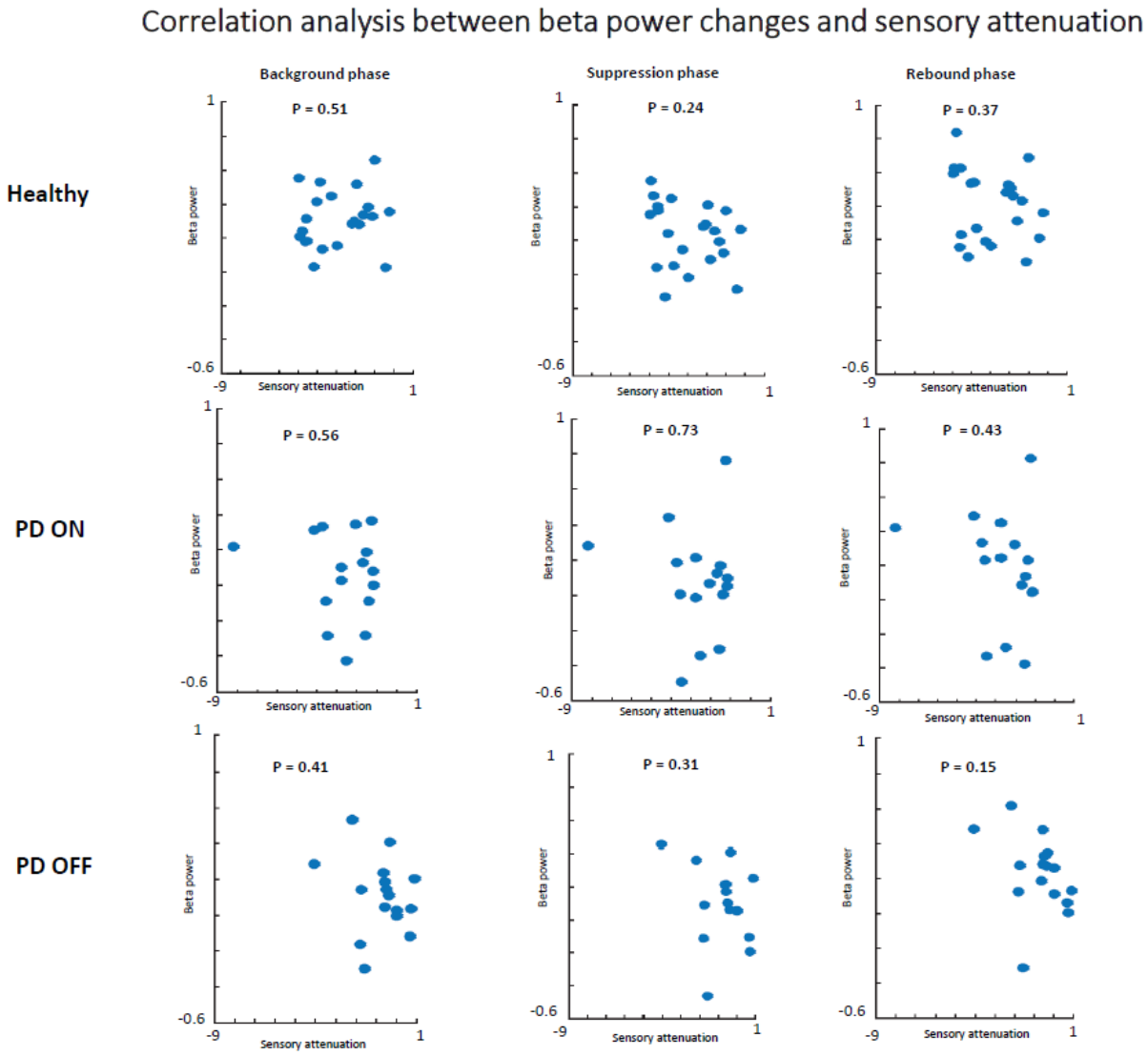


Figure 5.1.2.8. *Correlation analysis of beta oscillations amplitude modulation and sensory attenuation*

Having not found evidence for a relationship between the degree of SA and the changes in beta power, I tested the hypothesis that there was a relationship between beta oscillations amplitude and SSEP amplitude. The two measures were measured as a general phenomenon and not as function of the group. Therefore, I investigated if beta oscillations amplitude and SSEP amplitude were correlated in two groups: healthy + PD OFF and healthy + PD ON.

In the first analysed group including healthy and PD patients OFF medication, a positive correlation between beta power magnitude and SSEP amplitude was found in the rest condition in all selected time windows (background phase, $p=0.02$, $R^2 = 0.139$; suppression phase, $p=0.01$, $R^2 = 0.162$; rebound phase, $p=0.00$, $R^2 = 0.220$). In other words, lower amplitude of SEP was correlated with lower beta power amplitude.

However, this positive correlation seemed to be driven by the PD patients OFF medication. Indeed, when the two groups of participants were analysed separately, healthy subjects did not show any correlation between beta oscillations amplitude and SSEP amplitude at rest in each time window (background phase, $p=0.21$, $R^2 = 0.07$; suppression phase, $p=0.16$, $R^2 = 0.09$; rebound phase, $p=0.06$, $R^2 = 0.159$). Whereas, the PD OFF medication showed a significant correlation between the two measures at rest in all time windows (background phase, $p=0.02$, $R^2 = 0.304$; suppression phase, $p=0.01$, $R^2 = 0.335$; rebound phase, $p=0.01$, $R^2 = 0.371$) (figure 5.1.2.9).

In the movement condition the group of healthy subjects + PD OFF patients still showed a significant correlation between the two conditions in the background timing window ($p=0.03$, $R^2 = 0.113$) and a statistical trend in the

suppression phase (p=0.08, R^2 = 0.08) and in the rebound phase (p=0.08, R^2 = 0.08). Interestingly, this correlation was driven by the PD OFF patients. Indeed, when the two groups of participants were analysed separately the significant correlation was kept only by PD OFF medication. Indeed, the healthy controls group did not show any correlation in all time windows (background phase, p=0.41, R^2 = 0.03; suppression phase, p=0.69, R^2 = 0.008; rebound phase, p=0.46, R^2 = 0.02), whereas PD OFF medication showed significant correlation between beta oscillations modulations and SA in the 3 time windows (background phase, p=0.01, R^2 = 0.363; suppression phase, p=0.01, R^2 = 0.351; rebound phase, p=0.01, R^2 = 0.354)

These results might be explainable by the absence of SSEP attenuation in PD OFF at the onset of the movement. Therefore, the SSEP amplitude was the same in the two conditions in the PD OFF group and showed a correlation with the beta oscillations amplitude, which did not show any significant change as a function of condition in the previous analysis.

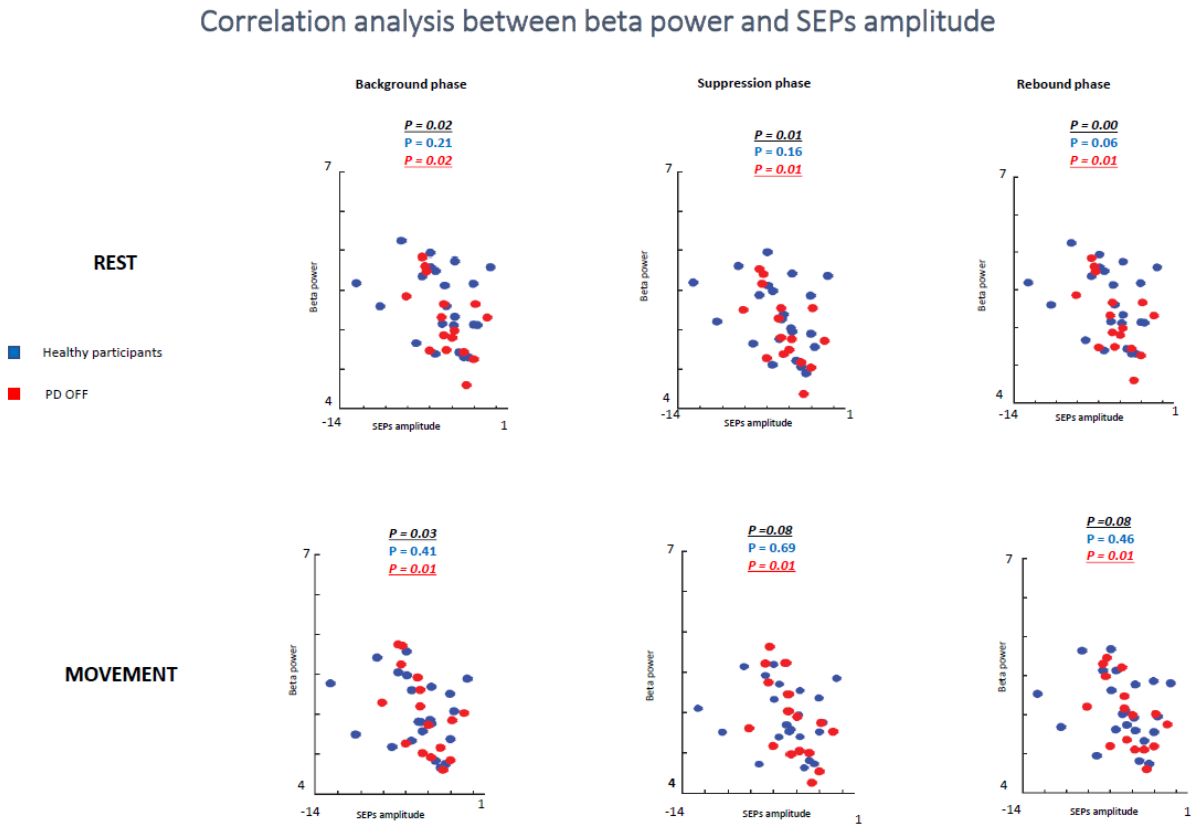


Figure 5.1.2.9. *Healthy + PD OFF*

In the second analysed group including healthy participants and PD patients ON medication a statistical trend of the correlation between beta oscillations amplitude and SSEP amplitude was found in the first two times windows (background phase, p=0.09, R^2 = 0.07; suppression phase, p=0.07, R^2 = 0.08) and a significant correlation in the rebound window in the rest condition (p=0.01, R^2 = 0.144). However, it is likely that this result was driven by the power of this bigger sample.

Indeed, when the two groups of participants were analysed separately, neither groups showed any significant correlations between the two measures in the rest condition in any time windows. Healthy subjects group did not show a significant correlation in the background phase (p=0.21, R^2 = 0.07) or in the suppression phase (p=0.16, R^2 = 0.09). There was a statistical trend in the rebound window (p=0.06, R^2 = 0.159). PD patients ON medication did not show significant correlation in background phase (p=0.62, R^2 = 0.08), suppression phase (p=0.44, R^2 = 0.06) and rebound phase (p=0.40, R^2 = 0.137) (figure 5.1.2.10).

In the movement condition, there was no significant correlation in all analysis (healthy participants + PD ON patients and separately healthy subjects and PD ON). Healthy + PD ON patients showed the following results: background phase, p=0.69, R^2 = 0.04; suppression phase, p=0.87, R^2 = 0.001; rebound window in the rest condition, p=0.88, R^2 = 0.001).

When the two groups of participants were analysed separately, neither groups showed any significant correlations between the two measures in the rest condition in any time windows. Healthy subjects group did not show a significant correlation in the background phase (p= 0.41, R^2 = 0.034) or in the suppression phase (p=0.69, R^2 = 0.008). There was a statistical trend

in the rebound window (p= 0.46, R^2 = 0.027). PD patients ON medication did not show significant correlation in background phase (p= 0.62, R^2 = 0.017), suppression phase (p=0.44, R^2 = 0.043) and rebound phase (p=0.40, R^2 = 0.050) (figure 5.1.10).

These results might be explainable by the presence of SSEP attenuation in both groups at the onset of the movement. Therefore, SSEP amplitude was lower at the onset of the movement compared to the magnitude at rest but beta does not change as function of condition, therefore the correlation was not significant.

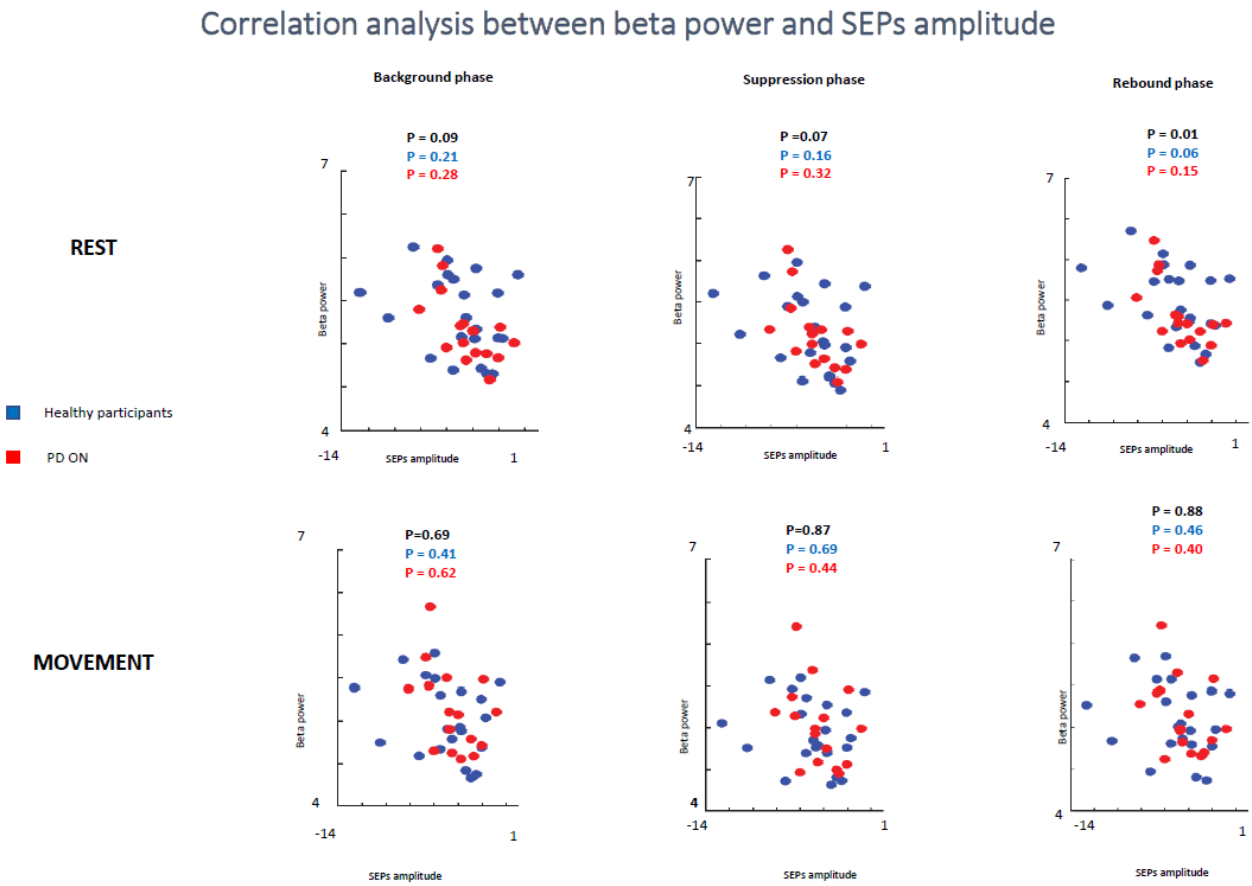


Figure 5.1.2.10. *Healthy + PD ON*

5.1.3 Discussion

The results of the first part of the study presented in this chapter confirmed the results presented in the previous study. In this chapter, a significant link was replicated between dopaminergic modulation and SA. Indeed, at movement onset PD patients OFF medication showed a lower SA compared to PD patients ON medication. Indeed, the mean difference of the N20-P25 amplitude between rest condition and movement condition was significantly different between PD patients OFF medication and ON medication ($p<0.05$).

The results replicated here were consistent with this prediction and were in support of the hypothesis that a failure in SA prior to movement onset contributes to the difficulties in movement initiation in PD. More specifically, is a pathology in modulating the gain of the afferent signal in PD patients underlies some clinical aspects of bradykinesia?

In line with previous studies our healthy subjects showed power in beta oscillations, which was attenuated prior the voluntary movement and augmented once the movement has ended.

I did not find any evidence for a relationship between the degree of SA and the change in beta power. This could be related to the size of our groups, which might produce a low statistical power. On the other hand, it is also possible that my results are due to the absence of link between the two phenomena. If this confirmed by further studies I might conclude that the modulation of these two mechanisms are independent. A significant relationship between SSEP amplitude and beta power was found.

These results are particularly interesting in the context of the active inference model of motor control, where SA is necessary for normal movements. Furthermore, our study is consistent with the with the sensory uncertainty (precision) model of SSEP generation but further work will be required to test this further.

The study suggested that cortical beta oscillations is modulated during voluntary movements but this modulation is not correlated with the modulation of SA. It is likely that two phenomena are involved in the motor control in different way and it is important to investigate further the potential correlations with other neuronal activity.

Chapter 6 – THE EFFECT OF MODULATING SOMATOSENSORY UNCERTAINTY ON MOTOR PERFORMANCE

6.1. Tendon vibration in the wrist during motor tasks

In the previous two chapters of my PhD, I have tested the hypothesis that SA was the neurophysiological mechanism underlying the bradykinesia and, then, I tested if there was any correlation with the beta oscillations, another phenomenon involved in motor control. As I explained in the previous chapters, Tan et al. (Tan et al., 2016) as well as Palmer et al. (C. Palmer et al., 2016) tested the hypothesis regarding a link between SA and uncertainty in the contest of the active inference framework. Therefore, if it is possible to modulate the uncertainty, intrinsically the SA is modulated, and it should be possible to elicited some effect on motor control. In this study of my PhD, I aimed to test if modulating the uncertainty of the proprioceptive signal, using high frequency peripheral vibration, I am able to determine a subsequent effect on motor control. It has previously been shown that high frequency vibration of forearm muscle tendons, which selectively activates muscle spindles (M. C. Brown, Enberg, & Matthews, 1967; Burke, Hagbarth, Lofstedt, & Wallin, 1976) produces the illusion that the arm is moving or has been displaced (Craske, 1977; Goodwin, McCloskey, & Matthews, 1972; McCloskey, 1973). The central nervous system incorrectly interprets this increased firing rate of muscle spindles as if the affected muscle is contracting, which generates uncertainty in the actual position of the limb. This has been demonstrated in a number of position-matching and pointing tasks all of which show increased error, or

reduced accuracy, following high-frequency peripheral vibration (Capaday & Cooke, 1983; Cordo et al., 1995; Inglis & Frank, 1990; Tsay, Giummarra, Allen, & Proske, 2016).

In this study I sought to understand how this interruption to normal proprioceptive processing could influence movement initiation. It was hypothesized that increasing proprioceptive uncertainty by giving high-frequency peripheral vibration prior to movement would improve motor initiation in both healthy subjects and PD patients in line with the theoretical accounts outlined above.

In summary, the aim of the series of experiments described here was to test the hypothesis that increasing somatosensory afferent uncertainty, using high frequency vibration, would lead to a measurable change in simple movements, reflecting faster movement onset and movement initiation. This was tested both in healthy subjects and patients with PD.

6.1.1. Methods

Behavioral study

Procedure and experimental design

Experiment 1

Eighteen right-handed healthy participants (9 men, 9 women, and mean age 30.5 years, range 19-39 years, Table 6.1.1.1) completed three different motor tasks using their right hand: 1) the box and blocks test (Mathiowetz, Volland, Kashman, & Weber, 1985); 2) the nine peg hole test (Oxford Grice et al., 2003); 3) a reaction time task (custom code written in MATLAB 2015a)

(Fig. 6.1.1.1.). For the box and blocks test, subjects were instructed to move as many blocks as they could from one box to another in 30 seconds. The total number of blocks moved was the dependent variable recorded. For the nine-hole peg task, subjects were instructed to place nine pegs into the nine holes as quickly as possible. For the reaction time task, subjects were instructed to look at a central fixation cross on a laptop screen and press the space bar on the keyboard when a green GO signal appeared. The time between the onset of the fixation cross and the green GO signal was either 500ms, 750ms or 1000ms and jittered between trials so the onset of the GO signal was not predictable. The mean reaction time over trials was the dependent variable for this task. Each task was repeated following two different conditions: 1) absence of external stimulus; and, 2) following 30 seconds of vibration on the right wrist. Each task began immediately after vibration stopped and the whole protocol (vibration followed by task) was repeated three times following each condition. Vibratory stimuli were delivered via an electromagnetic mechanical stimulator (Ling Dynamics System) with a 3-cm-diameter circular probe. Participants lightly rested the anterior surface of their wrist on top of the probe just proximal to the crease in the wrist and their arm was supported with a pillow. The vibration frequency was 80Hz; this was based on previous research showing that vibration at this frequency drives kinaesthetic illusions and thus modulates proprioceptive uncertainty (Goodwin et al., 1972; McCloskey, 1973).

Each motor task was repeated three times following each vibration condition. The order of conditions was counterbalanced across participants in each group. The study was approved by the local institutional ethics

committee, the East of Scotland Research Ethics Service. Written informed consent was obtained from all participants.

Healthy participants	Age (y)	Gender
1	32	F
2	24	F
3	31	F
4	23	F
5	31	M
6	29	M
7	31	M
8	19	M
9	21	M
10	31	F
11	31	F
12	33	M
13	39	M
14	38	M
15	38	M
16	34	F
17	33	F
18	32	F
Mean ± SD	30.5 ± 5.6	F9/M9

Table 6.1.1.1*. Demographic characteristics of healthy subjects included in the experiment 1 and experiment 2 of the behavioural study (y _ years; SD _ standard deviation).*

Experiment 2

The eighteen healthy participants previously recruited for experiment 1 were re-recruited for experiment 2 and performed the blocks and box test, the nine peg hole test and the reaction time task with their right hand following three different conditions: 1) absence of vibratory stimuli; 2) following 30 seconds of 80 Hz vibration on the right wrist; 3) following 30 seconds of 80 Hz vibration on the left wrist. This latter condition acted as an active control condition. Each motor task was repeated three times following each vibration condition. The order of conditions was counterbalanced across participants in each group. Written informed consent was obtained from all participants.

Experiment 3

Eighteen naïve right-handed healthy participants (9 men, 9 women, and mean age 30.2 years, range 20-40 years, Table 6.1.1.2) completed four different motor tasks using their right hand: 1) the box and blocks test; 2) the nine peg hole test; 3) a reaction time task; 4) one minute of right hand tapping with the cybernetic glove (Fig. 6.1.1.1.). For the tapping task participants were instructed to tap their right index finger against their thumb as fast as they could with the largest amplitude tap. Hand movements were recorded with a Cyberglove. Offline the amplitude and frequency of the tapping between the thumb and finger of the right hand was calculated. Each task was repeated following three different conditions: 1) absence of vibration; 2) following 30 seconds of 80 Hz vibration on the right wrist; 3) following 30 seconds of 20 Hz vibration on the right wrist. This latter condition acted as an alternative active vibration control, which, in this

experiment, was applied to the same wrist that completed the tasks. Each motor task was repeated three times following each vibration condition. The order of conditions was counterbalanced across participants in each group. Written informed consent was obtained from all participants.

Healthy participants	Age (y)	Gender
1	36	M
2	35	F
3	31	F
4	30	F
5	31	M
6	29	F
7	31	F
8	26	F
9	20	M
10	25	M
11	27	F
12	23	M
13	40	M
14	32	F
15	35	M
16	21	F
17	40	M
18	33	M
Mean $\pm$ SD	30.2 $\pm$ 5.8	F9/M9

Table 6.1.1.2. *Demographic characteristics of healthy subjects included in the experiment 3 of the behavioral study (y _ years; SD _ standard deviation).*

Experiment 4

Eighteen patients with idiopathic PD (11 men, 7 women, mean age 65.5 years, range 49–78 years, Table 6.1.1.3) were involved in this experiment. Idiopathic PD was diagnosed according to the UK PD Society Brain Bank criteria (A. J. Hughes et al., 1992) and further confirmed by abnormal dopamine transporter SPECT in all patients. None of the patients had disabling tremor. None of the participants were on any non-PD medications that could affect the measurements performed. All participants were right-handed. Clinical disease severity was assessed with the motor section (items 3.1–3.18) of the UPDRS (Goetz et al., 2008). Patients were assessed in the ON state one hour after taking levodopa and 2 hours of taking dopamine agonists. The eighteen PD patients completed the same protocol as in experiment 3. Written informed consent was obtained from all participants.

Patients	Age (y)	Gender	Disease duration (y)	Motor UPDRS items ON state (right upper limb)	Treatments
1	52	M	10	8	L + D
2	49	M	3	6	L + D
3	72	F	3	11	L
4	70	M	3	9	L
5	73	M	10	8	L + D
6	60	F	5	4	L + D
7	61	F	9	12	L
8	70	F	5	5	L + D
9	65	F	10	12	L
10	75	M	6	4	L + D
11	53	M	2	10	L
12	73	M	10	4	L + D
13	72	M	10	11	L
14	65	M	8	9	L + D
15	78	M	10	9	L
16	61	M	6	6	L
17	64	F	6	5	L + D
18	67	F	9	8	L + D
Mean $\pm$ SD	65.5 $\pm$ 8.3	F7/M11	6.9 $\pm$ 2.9	8.05 $\pm$ 2.94	

Table 6.1.1.3. *Clinical and demographic characteristics of patients with Parkinson disease (y_ years; SD _ standard deviation; UPDRS_ Unified Parkinson's Disease Rating Scale).*

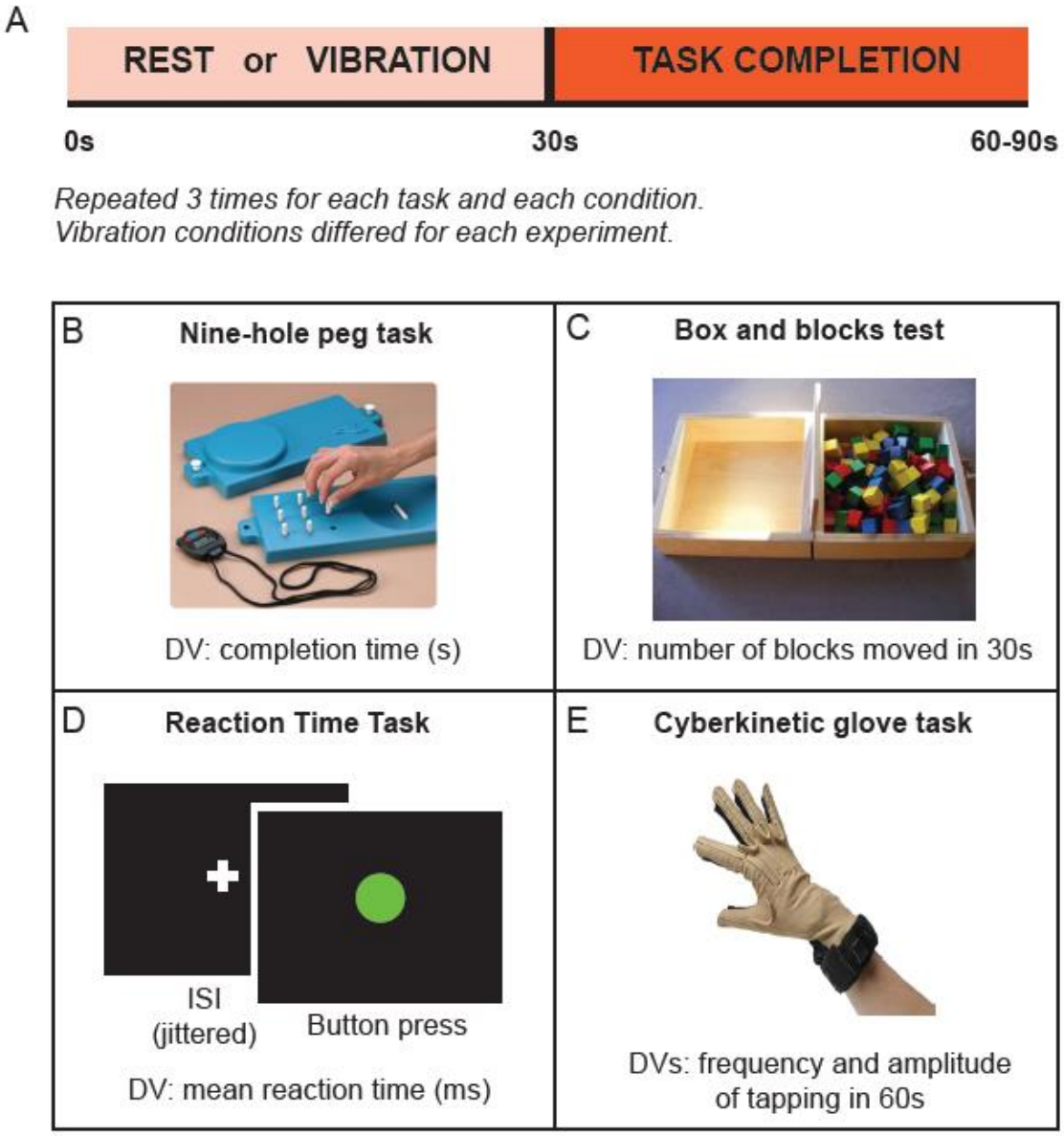


Figure 6.1.1.1. *Flow chart of behavioral experiment protocol.*

A) In each experiment 30 seconds of 80Hz vibration or no vibration or a control condition was given prior to completing a motor task. We tested the effect of high-frequency vibration on the completion time of several motor tasks. Each condition (vibration, rest or control) as well as each task was repeated three times. Particularly, Experiment 1 tested two conditions: 30 seconds vibration at 80 Hz on the right wrist vs no vibration; Experiment 2 tested three conditions: 30 seconds vibration at 80 Hz on the right wrist, no vibration and 80 Hz on the left wrist (control condition); Experiment 3 and Experiment 4 (PD patients) tested the following three conditions: 30 seconds vibration at 80 Hz on the right wrist, no vibration and 20 Hz on the right wrist (control condition). All experiments except experiment 4 used healthy subjects. In all experiments, the motor performance was measured throughout using the following three tasks: 9 peg hole test (B), box and blocks task (C) and reaction time test (D).
In the experiment 3 as well as 4, we also measured the amplitude and frequency of the tapping with the cyber glove (E).

Data analysis

The following dependent variables were recorded for each motor task tested across the four experiments described:

- Box and blocks test: mean number of cubes moved from one box to the other box in 30 seconds.

- Nine peg hole test: mean completion time of the test (seconds)

- Reaction time test: mean reaction time (milliseconds)

- Tapping test with the cyber glove: mean frequency and amplitude of the tapping over 1 minute of time window.

These were the measures of movement performance in our study. Firstly, we calculated the mean value as well as the corrected mean value for each parameter. The mean corrected values removed the between subject effect by removing the mean value across conditions for each subject.

Experiment 1 only included two conditions (80 Hz vibration vs no vibration), therefore we performed a paired samples t-test to determine the effect of 80Hz vibration on the mean of each dependent variable compared to the no vibration condition. For experiments 2, 3 and 4, a one-way repeated measure analysis of variance (rmANOVA) was conducted for each dependent variable using the following factor: condition (vibration, no vibration, control condition). Post-hoc tests were conducted with Bonferroni corrections for multiple comparisons. P values less than 0.05 were considered to be significant. SPSS Statistics software (version 22.0.0) was used for the statistical analysis data from the blocks and box test and the

nine-hole peg task. Custom code written in Matlab (version 2015a) was used to analyse the reaction time results and the frequency and amplitude of the tapping.

6.1.2. Results

Experiment 1

There was a significant difference in the mean completion time of the nine-hole peg test between the two conditions (absence and presence of vibration; t (17) = 2.532, p = 0.02). After 30 seconds of 80 Hz peripheral vibration, the nine-hole peg task was completed in a faster time (11.73 ± 1.81seconds) than after no vibration (12.63 ± 0.89 seconds; Fig. 6.1.2.1 A & B). No significant difference was found in the performance of the box and blocks test between the two conditions although the trend was for more boxes to be moved in the same time period following 80 Hz vibration (36 ± 6 boxes) than after no vibration (34 ± 5 boxes), (t (17) = -1.822, p = 0.08) (Fig. 6.1.2.1 C&D). The mean reaction time was significantly faster in the reaction time task following 80 Hz vibration (302.83 ± 52.82ms) than after no vibration (318.33 ± 51.39 ms), (t (17) = 3.046, p = 0.007) (Fig. 6.1.2.1 E&F).

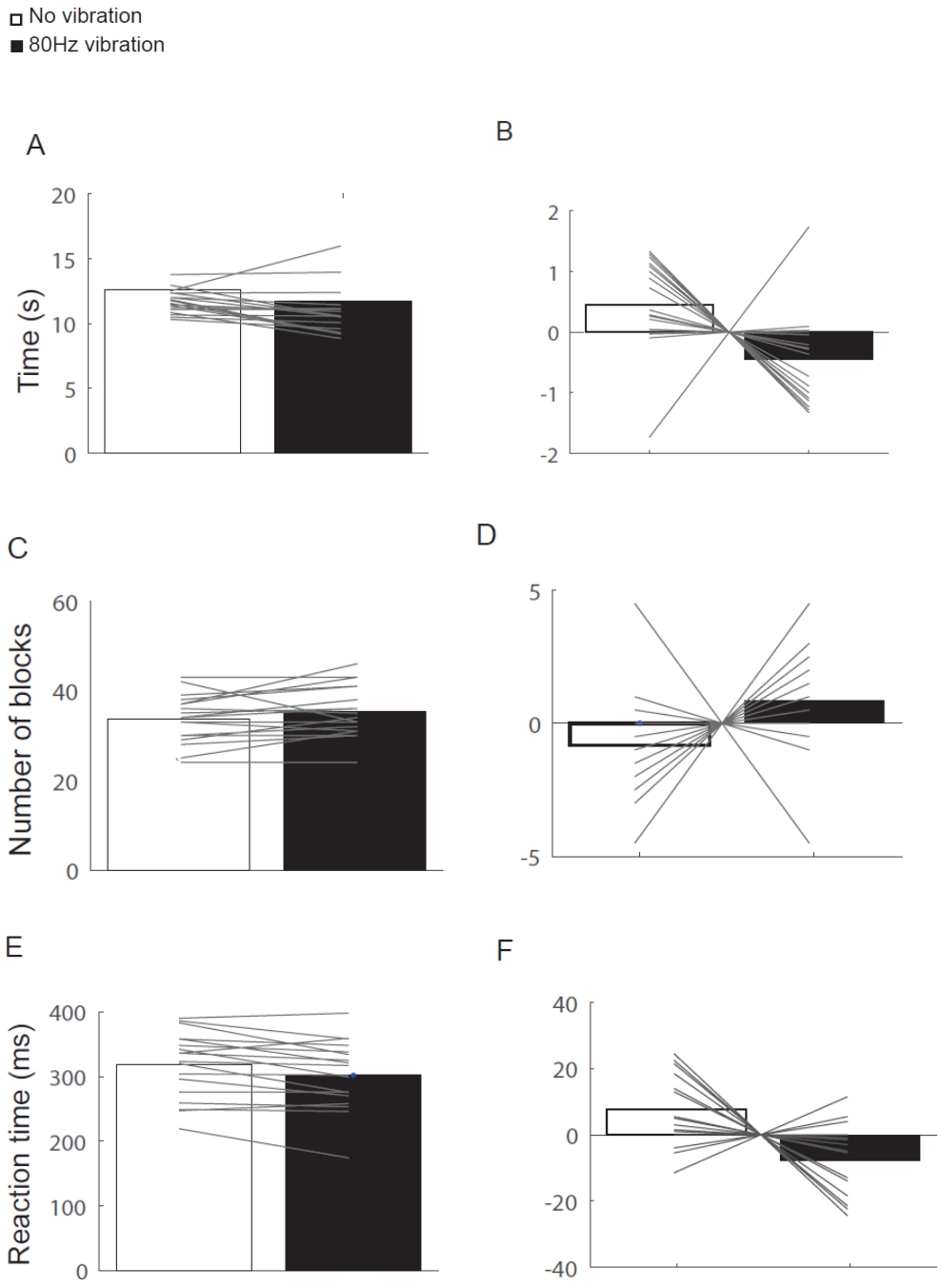


Figure 6.1.2.1. *The figure shows the results of experiment 1.*

Healthy subjects show improved motor performance following 80Hz vibration compared to no vibration. Bar graphs show the mean and the corrected mean of completion time for the nine hole peg task (A, B), of the number of the blocks moved in 30 seconds on the blocks and box test (C, D), and of the reaction time task (E, F). 80Hz vibration (black bars). No vibration (white bars). Each grey line represents a participant. Thus, the grey line joints the two values related to the two different experimental conditions of each participant.

Experiment 2

Having demonstrated in Experiment 1 that 30 seconds of 80 Hz vibration applied to the musculotendinous junction of the right wrist had a significant effect on movement times compared to no vibration, Experiment 2 aimed to introduce a control condition to discount a placebo effect.

A repeated measures ANOVA revealed a significant main effect of condition on the mean completion time of the nine-peg hole test, ($F(2, 34) = 31.686$, $p < 0.001$, $Eta^2 = 0.651$) (Fig. 6.1.2.2. A&B). Post-hoc pairwise comparisons corrected for multiple comparisons revealed a significant difference between mean completion time following 80 Hz vibration on the right wrist (10.94 ± 1.14 seconds) and no vibration (12.21 ± 1.45 seconds), ($t(17) = 7.351$, $p < 0.001$), and between 80 Hz vibration on the right wrist and 80 Hz vibration on the left wrist (12.17 ± 1.03 seconds), ($t(17) = -6.483$, $p < 0.001$). There was no significant difference between mean completion time following 80Hz vibration on the left wrist and no vibration, ($t(17) = 0.257$, $p = 0.8$).

For the box and blocks test, a repeated measures ANOVA showed a significant main effect of condition on motor performance, ($F(2, 34) = 116.978$, $p < 0.001$, $Eta^2 = 0.873$) (Fig. 6.1.2.2. C&D). Post-hoc pairwise comparisons corrected for multiple comparisons revealed a significant difference between the number of cubes moved from one box to the other following 80 Hz vibration on the right wrist (38 ± 4 boxes) and no vibration (35 ± 4 boxes), ($t(17) = -11.717$, $p < 0.001$), as well as between 80 Hz vibration on the right wrist and 80 Hz vibration on the left wrist (34 ± 5 boxes), ($t(17) = 11.985$, $p < 0.001$). There was no significant difference

between the performance of the test following 80 Hz vibration on the left wrist and no vibration, (t (17) = -0.236, p = 0.8). For the reaction time task, there was no significant main effect of condition on mean reaction time (F (2, 34) = 1.856, p = 0.1, Eta^2 = 0.098). There was no significant difference between reaction time following 80 Hz vibration and no vibration (t (17) = 1.3, p = 0.2). There was no significant difference between the mean reaction times following 80 Hz vibration on the right wrist and 80 Hz vibration on the left wrist (t (17) = -1.544, p = 0.1) as well as between no vibration and 20 Hz vibration (t (17) = -0.512, p = 0.6) (Fig. 6.1.2.2 E&F).

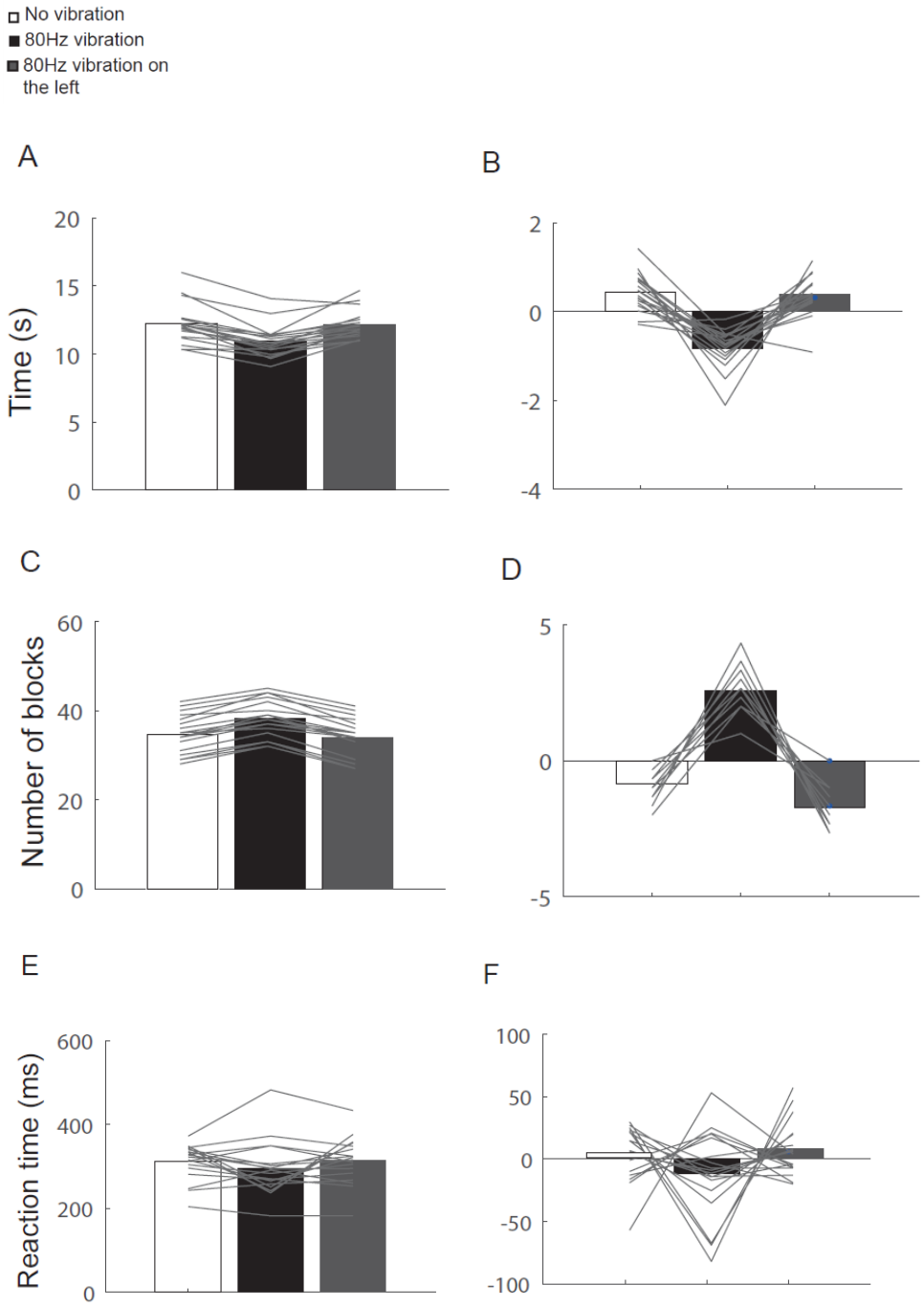


Figure 6.1.2.2 *The figure shows the results of experiment 2.*

Healthy subjects show improved motor performance following 80Hz vibration specifically to the moving hand compared to the non-moving hand. Bar graphs show the mean and the corrected mean of completion time for the nine hole peg task (A, B), of the number of the blocks moved in 30 seconds on the box and bocks test (C, D), and of the reaction time task (E, F). 80Hz vibration to the wrist of the moving hand (black bars). 80Hz vibration to the wrist of the non-moving hand (grey bars). No vibration (white bars). Each grey line represents a participant. Thus, the grey line joints the three values related to the three different experimental conditions of each participant.

Experiment 3

Having demonstrated in Experiments 1&2 that 30 seconds of 80 Hz vibration applied to the musculotendinous junction of the right wrist had a significant effect on motor performance, Experiment 3 aimed to test whether the frequency of stimulation was critical for the observed modulations in motor performance and in turn provide a more optimal control condition. To this end we investigated the effect of vibration at 80 Hz and 20 Hz to control for any potential placebo effect of vibration at the wrist of the hand completing the motor task.

Repeated measures ANOVA revealed a significant main effect of condition on the performance of the nine-peg hole test, ($F(2, 34) = 32.025$, $p < 0.001$, $Eta^2 = 0.653$). Post-hoc pairwise comparisons, corrected for multiple comparisons, revealed a significant difference between mean movement speed following 80 Hz vibration (11.01 ± 1.58 seconds) and no vibration (12.35 ± 1.31 seconds), ($t(17) = 5.899$, $p < 0.001$), as well as between 80 Hz vibration and 20 Hz vibration (12.38 ± 1.46 seconds), ($t(17) = -11.064$, $p < 0.001$). There was no significant difference in mean movement speed following 20 Hz vibration and no vibration, ($t(17) = -1.139$, $p = 0.8$) (Fig. 6.1.2.3 A&B).

For the box and blocks test, a repeated measures ANOVA showed a significant main effect of condition on motor performance, ($F(2, 34) = 74.478$, $p < 0.001$, $Eta^2 = 0.814$). Post-hoc pairwise comparisons, corrected for multiple comparisons, revealed a significant difference between the number of cubes moved following 80 Hz vibration (34 ± 7 boxes) and no vibration (29 ± 5 boxes), ($t(17) = -11.228$, $p < 0.001$), as well as between

80 Hz vibration and 20 Hz vibration (29 ± 6 boxes), ($t(17) = 10.409$, $p < 0.001$). There was no significant difference between the performance of the test following baseline and 20 Hz vibration, ($t(17) = -0.325$, $p = 0.7$) (Fig. 6.1.2.3. C&D).

For the reaction time test, a repeated measures ANOVA showed a significant main effect of condition on motor performance, ($F(2, 34) = 6.416$, $p = 0.004$, $Eta^2 = 0.274$). Post-hoc pairwise comparisons, corrected for multiple comparisons, revealed a significant difference in reaction time following 80 Hz vibration on the right wrist (283.17 ± 39.408 ms) and no vibration (308.83 ± 60.601 ms), ($t(17) = 3.044$, $p = 0.007$), as well as between 80 Hz vibration and 20 Hz vibration (301.67 ± 57.455 ms), ($t(17) = -3.128$, $= 0.006$). There was no significant difference between the performance of the test following baseline and 20 Hz vibration, ($t(17) = 0.894$, $p = 0.3$) (Fig. 6.1.2.3 E&F).

In this group, the tapping test was performed and the kinematics of the hand movements were measured using a cyber glove. Two measures were calculated: the amplitude and the frequency of the taps. A repeated measures ANOVA revealed no significant main effect of condition on the amplitude of the tapping, ($F(2, 34) = 0.663$, $p = 0.5$, $Eta^2 = 0.038$) (Fig. 6.1.2.3 L&K). However, a repeated measures ANOVA showed a significant main effect of condition on the frequency of the tapping, ($F(2, 34) = 7.838$, $p = 0.002$, $Eta^2 = 0.316$) (Fig. 6.1.2.3 G&H). Post-hoc pairwise comparisons, corrected for multiple comparisons, revealed a significant difference between the tapping frequency following 80 Hz vibration (2.63 Hz ± 0.61) and no vibration (2.16 Hz ± 0.46), ($t(17) = -3.981$, $p = 0.001$), as well as

between 80 Hz vibration and 20 Hz vibration (2.48 Hz ± 0.74), ($t(17) = 2.278$, $p = 0.001$). There was no significant difference between the performance of the test following 20 Hz vibration and no vibration, ($t = -1.464$, $p = 0.1$).

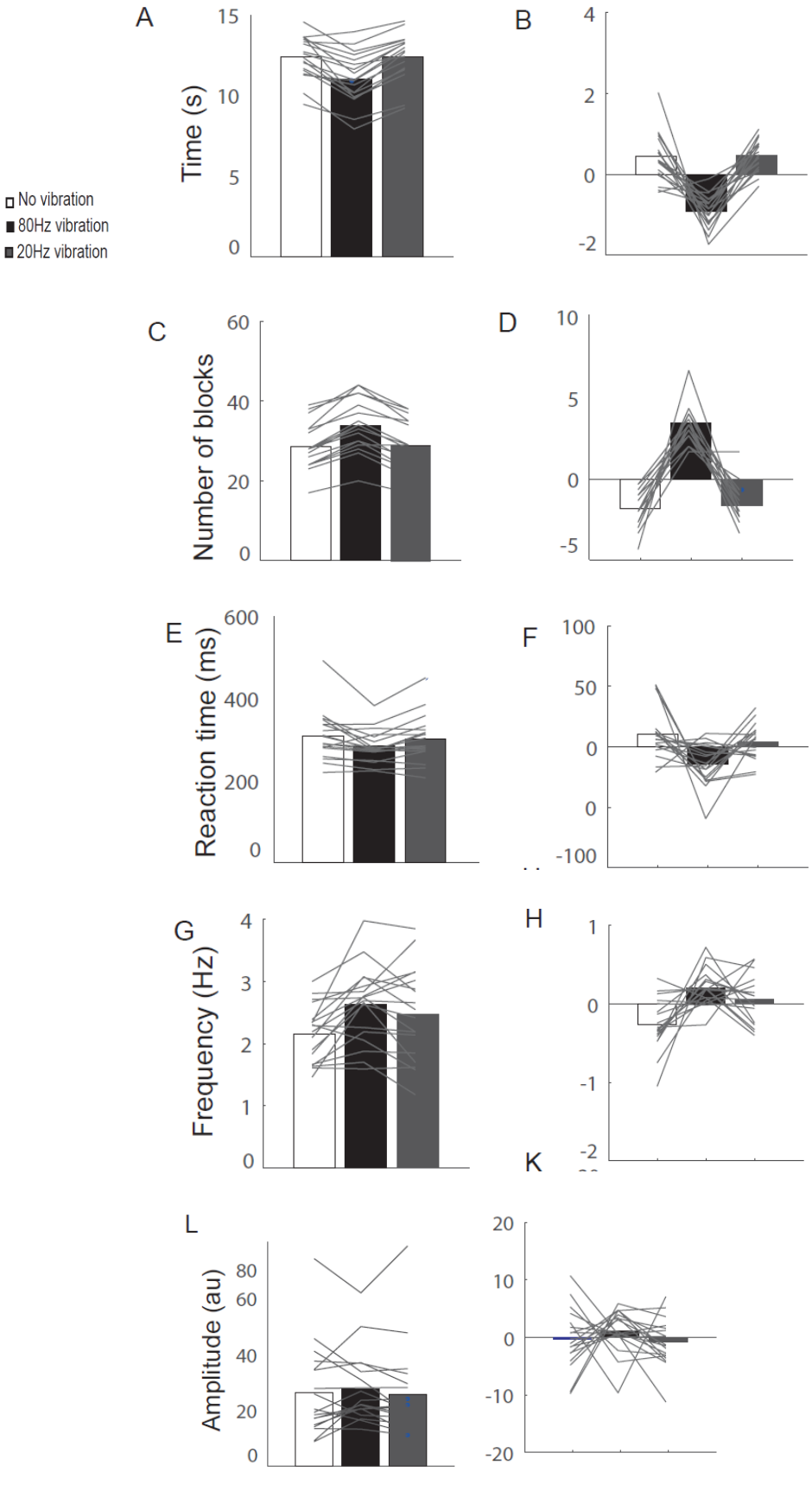

No vibration
80Hz vibration
20Hz vibration
A
Time (s)
B
C
Number of blocks
D
E
Reaction time (ms)
F
G
Frequency (Hz)
H
K
L
Amplitude (au)

Figure 6.1.2.3. *The figure shows the results of experiment 3.*

Healthy subjects show improved motor performance following 80Hz vibration but not to 20Hz vibration. Bar graphs show the mean and the corrected mean of completion time for the nine hole peg task (A, B), of the number of the blocks moved in 30 seconds on the box and blocks task (C, D), of the reaction time task (E, F), of tapping frequency measured with a cyberglove (G, H) and of tapping amplitude (I, J). 80Hz vibration (black bars). 20Hz vibration (grey bars). No vibration (white bars). Each grey line represents a participant. Thus, the grey line joints the three values related to the three different experimental conditions of each participant.

Experiment 4

The previous three experiments demonstrated significant modulations in different movement parameters of the right hand following 30 seconds of 80 Hz vibration applied to the right wrist. This is consistent with the hypothesis tested that increasing noise in the somatosensory afferent signal would result in faster movements and movement initiation in young healthy controls. In Experiment 4 we tested the hypothesis that vibration at 80Hz applied to the right wrist would improve motor performance in participants with PD.

A repeated measures ANOVA revealed a significant main effect of condition on the performance of the nine-peg hole test, ($F(2, 34) = 58.355$, $p < 0.001$, $Eta^2 = 0.774$). Post-hoc pairwise comparisons revealed a significant difference between mean movement speed following 80 Hz vibration (15.52 ± 3.82 seconds) and no vibration (19.12 ± 4.45 seconds), ($t(17) = 8.229$, $p < 0.001$) as well as 80 Hz vibration and 20 Hz vibration (19.35 ± 4.65 seconds), ($t(17) = -9.485$, $p < 0.001$). There was no significant difference between mean movement speed following no vibration and 20Hz vibration, ($t(17) = -0.682$, $p = 0.5$) (Fig. 6.1.2.4 A&B).

Furthermore, for the blocks and box test, a repeated measures ANOVA showed a significant main effect of condition on motor performance, ($F(2, 34) = 45.234$, $p < 0.001$, $Eta^2 = 0.727$). Post-hoc pairwise comparisons revealed a significant difference between the number of cubes moved following 80Hz vibration (28 ± 5 boxes) and no vibration (22 ± 4 boxes), ($t(17) = -7.262$, $p < 0.001$), as well as between 80 Hz vibration and 20 Hz vibration (22 ± 4 boxes), ($t(17) = 8.321$, $p < 0.001$). There was no significant

difference between the performance of the test following no vibration and 20 Hz vibration, (t (17) = -0.416, p = 0.6) (Fig. 6.1.2.4 C&D).

Regarding reaction time task, a repeated measures ANOVA showed a significant main effect of condition on the reaction time, (F (2, 34) = 4.078, p = 0.02, Eta^2 = 0.193). Post-hoc pairwise comparisons revealed no significant difference between mean reaction time following 80 Hz vibration (355.89 ± 67.77 ms) and no vibration (412.28 ± 116.53 ms), (t (17) = 2.310, p = 0.03) and a significant difference between 80 Hz vibration and 20 Hz vibration (434.61 ± 129.81ms), (t (17) = -2.496, p = 0.002). There was no significant difference between the performance of the test following 20 Hz vibration and no vibration, (t (17) = -0.775, p = 0.4) (Fig. 6.1.2.4 E&F).

A repeated measures ANOVA showed a significant main effect of condition on the frequency of tapping, (F (2, 34) = 11.623, p < 0.001, Eta^2 = 0.406). Post-hoc pairwise comparisons corrected for multiple comparisons revealed a significant difference between tapping frequency following 80 Hz vibration (2.354 Hz ± 0.58) and no vibration (1.848 Hz ± 0.48), (t (17) = -5.313, p < 0.001), but not between 80 Hz vibration and 20 Hz vibration (2.223 Hz ± 0.56), (t (17) = 1.090, p = 0.2). There was a significant difference between the frequency of tapping following 20 Hz vibration and no vibration (t (17) = -3.428, p = 0.003) (Fig. 6.1.2.4 G&H). There was a statistical trend of the effect of condition on the amplitude of the tapping, (F (2, 34) = 3.090, p = 0.05, Eta^2 = 0.154) (Fig. 6.1.2.4 I&J). There was a significant difference between the amplitude of the tapping following 80 Hz vibration (19.42 a.u. ± 8.85) and no vibration (16.91a.u. ± 7.35) (t (17) = -2.377, p = 0.02). There was a statistical trend in the difference between the amplitude of the tapping

following 80 Hz vibration and 20 Hz (16.43 a.u. ± 8.27) ($t(17) = 2.077$, $p = 0.05$). There was no difference between no vibration condition and 20 Hz vibration ($t(17) = 0.356$, $p = 0.7$).

In order to determine if there were any significant differences in motor performance following 80 Hz vibration between the 18 healthy subjects that participated in Experiment 3 and the 18 PD patients, a repeated measures ANOVA was conducted for each behavioral task with group as a between subject's factor and condition (no vibration, 80Hz vibration to the right wrist and 20 Hz vibration) as a within-subjects factor. The motor performance of healthy controls was significantly different from PD patients on the nine-hole peg task ($F(1,34) = 33.906$, $p < 0.001$, $Eta^2 = 0.499$), the box and blocks test ($F(1,34) = 14.637$, $p = 0.001$, $Eta^2 = 0.301$), the simple reaction time task ($F(1,34) = 20.481$, $p < 0.001$, $Eta^2 = 0.376$) and amplitude of tapping ($F(1,34) = 5.471$, $p = 0.02$, $Eta^2 = 0.139$), but not in the frequency of tapping ($F(1,34) = 2.774$, $p = 0.1$, $Eta^2 = 0.075$).

Overall, PD patients produced slower movements than healthy controls (Table 6.1.2.1).

	PD patients	Healthy subjects
Peg-hole task[*]		
- no vibration	19.12 ± 4.45	12.35 ± 1.31
-80 Hz vibration	15.52 ± 3.82	11.01 ± 1.58
-20 Hz vibration	19.35 ± 4.65	12.38 ± 1.46
Box and blocks test[*2]		
- no vibration	22 ± 4	29 ± 5
-80 Hz vibration	28 ± 5	34 ± 7
-20 Hz vibration	22 ± 4	29 ± 6
Reaction time[*3]		
- no vibration	412.28 ± 116.53	308.33 ± 60.61
-80 Hz vibration	355.89 ± 67.77	283.16 ± 39.41
-20 Hz vibration	434.61 ± 129.81	301.66 ± 57.45
Tapping frequency[*4]		
- no vibration	1.848 ± 0.48	2.16 ± 0.46
-80 Hz vibration	2.354 ± 0.58	2.63 ± 0.61
-20 Hz vibration	2.223 ± 0.56	2.48 ± 0.74
Tapping amplitude[*5]		
- no vibration	16.91 ± 7.35	26.27 ± 16.23
-80 Hz vibration	19.43 ± 8.85	27.68 ± 12.46
-20 Hz vibration	16.43 ± 8.27	25.65 ± 16.10

* completion time in seconds

*2 number of boxes moved in 30 seconds

*3 completion time in milliseconds

*4 frequency in Hz

*5 amplitude in a.u

Table 6.1.2.1. *Motor performance of the PD patients and the healthy subjects recruited in experiment 3.*

In support of previous results, there was a significant main effect of condition in all motor tasks (all $p < 0.003$) except the amplitude of tapping ($p = 0.06$). The interaction between condition and group was not significant for any of the motor tasks ($p > 0.05$) suggesting the magnitude of improvement following 80 Hz vibration was similar between the groups.

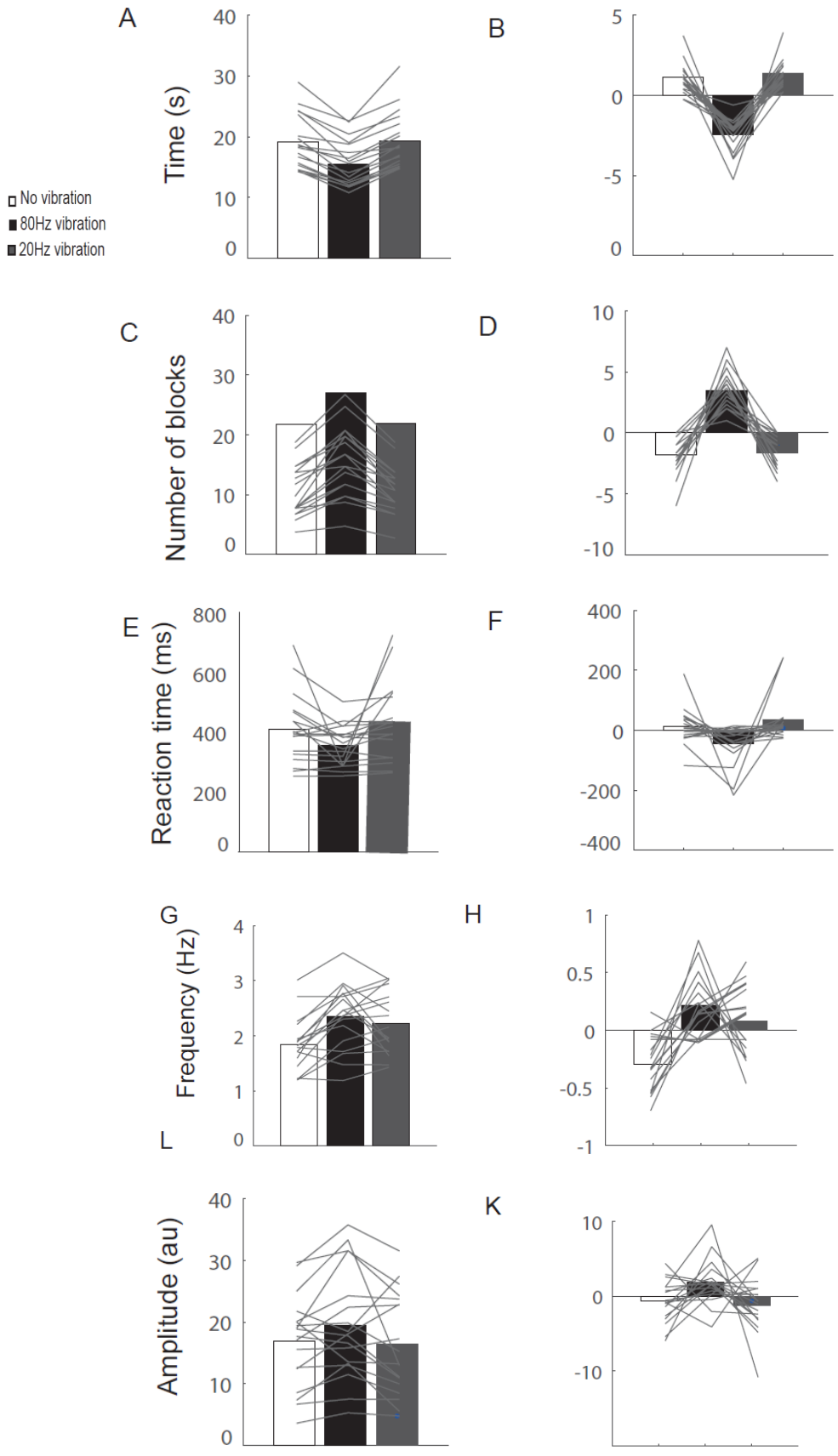

A
B
C
D
E
F
G
H
L
K
No vibration
80Hz vibration
20Hz vibration
Time (s)
Number of blocks
Reaction time (ms)
Frequency (Hz)
Amplitude (au)

Figure 6.1.2.4. *The figure shows the results of experiment 4.*

Parkinson's Disease patients show improved motor performance following 80Hz vibration but not 20Hz. Bar graphs show the mean and the corrected mean of completion time for the nine peg-hole (A, B), of the number of the blocks moved in 30 seconds (C, D), of the reaction time task (E, F), of tapping frequency (G, H) and tapping amplitude (I, J). Each grey line represents a participant. Thus, the grey line joints the three values related to the three different experimental conditions of each participant.

6.1.3. Discussion

The study of this chapter aimed to test the hypothesis that increasing proprioceptive uncertainty would lead to improvements on a number of motor control tasks. A peripheral vibrating stimulus at 80 Hz was used to change the proprioceptive signal in order to alter the uncertainty of the afferent signal. As hypothesized, in general 30 seconds of 80 Hz peripheral vibration applied to the right wrist of a total of 54 healthy controls reproducibly improved performance related to movement speed across 4 separate experiments on a number of motor control tasks (see table below). Improved performance on all motor tasks (except the amplitude of finger tapping) was also seen for a sample of 18 PD patients ON medication. Interestingly, Dr Palmer, a member of Dr Kiner's lab found that EEG data revealed a significant decrease in beta oscillatory activity (15-30Hz) over the contralateral sensorimotor cortex at the onset and offset of 80Hz vibration. In contrast, peripheral vibration at 20Hz had no effect on motor performance and caused no modulation in beta oscillatory activity.

The study described in this chapter clearly showed that peripheral vibration at 80 Hz improved motor performance on a variety of motor control tasks. In light of the results of Dr Palmer's study, I hypothesized that this improvement may have been driven by a modulation of beta oscillatory activity over sensorimotor cortex.

In summary, in this study, I tested the effect of vibration with up to five different movement parameters in up to five separate experiments. For ease of comparison, I have collated these results in the table 6.1.3.1.

Furthermore, I have summarized the results of the omnibus statistics for each task in the figures 6.1.2.5, 6.1.2.6, 6.1.2.7.

	9 Peg- hole test		**Box and blocks test**		**Reaction time test**		**Frequency of fingers tapping**		**Amplitude of fingers tapping**	
	ANOVA	t-test baseline vs 80 Hz	ANOVA	t-test baseline vs 80 Hz	ANOVA	t-test baseline vs 80 Hz	ANOVA	t-test baseline vs 80 Hz	ANOVA	t-test baseline vs 80 Hz
Exp.1		t (17) =2.532 p = 0.02		t (17)=1.822 p = 0.08		t (17)=3.046 p = 0.007				
Exp. 2	F(2,34)=31.686 p = 0.000	t (17) =7.351 p = 0.000	F(2,34)=116.978 p = 0.000	t(17)=11.717 p = 0.000	F(2,34)=1.856 p = 0.1	t (17) =1.3 p = 0.2				
Exp. 3	F(2,34)=32.025 p = 0.000	t (17) =5.899 p = 0.000	F (2, 34) = 74.478 p = 0.000	t(17)= - 11.228 p = 0.000	F(2, 34) = 6.416 p = 0.004	t (17) =3.044 p = 0.007	F(2,34) =7.838 p = 0.002	t (17)= - 3.981 p = 0.001	F(2,34)= 0.663 p = 0.5	t(17) = - 0.735 p = 0.4
Exp. 4	F (2, 34) =58.355 p = 0.000	t (17) = 8.229 p = 0.000	F (2, 34) = 45.234 p = 0.000	t (17) = -7.262 p = 0.000	F (2, 34) = 4.078 p = 0.02	t (17) = 2.310 p = 0.03	F (2, 34) = 11.623 p = 0.000	t (17) = - 5.313 p = 0.000	F (2, 34) = 3.090 p = 0.05	t (17) = - 2.377 p = 0.02
Exp. 5	F (2,34) = 32.758 p = 0.000	t (17) = 7.480 p = 0.000								

Table 6.1.3.1. *Effect of vibration with up to five different movement parameters in up to five separate experiments.*

All experiments contained a baseline (no vibration) and 80 Hz vibration of the right wrist conditions. The table contains both the result of the rmANOVA (as described above in the text) and the direct t-test testing the difference between baseline and 80 Hz. In every replication there was a significant difference in the time taken to complete the 9 Peg Hole task in the baseline and 80 Hz conditions (Table 6.1.3.1.). For the blocks and box test there was a significant effect in Experiments 2, 3 and 4 but only a trend to significance in Experiment 1. There were no significant differences in the magnitude of the difference between baseline and 80 Hz between the different experiments. For the reaction time test there was a significant effect in Experiments 1, 3 and 4 but no significant effect in Experiment 2. There were no significant differences in the magnitude of the difference between baseline and 80 Hz between the different experiments. Given this it is only possible to conclude that the failure to observe a significant effect in one of the four experiments simply reflects the natural variance in this measure as there was no systematic difference in the magnitude of the effects between conditions.

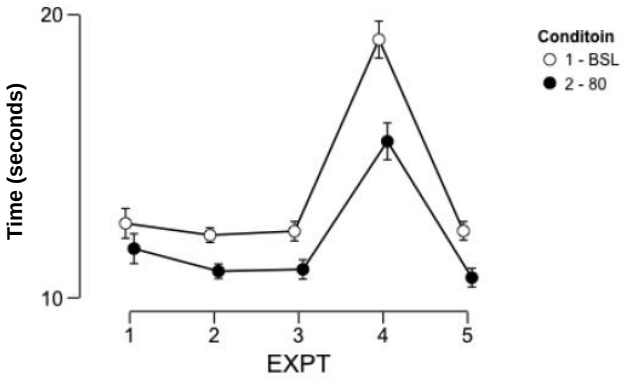


Figure 6.1.3.1. Omnibus statistics for 9 Peg Hole Test

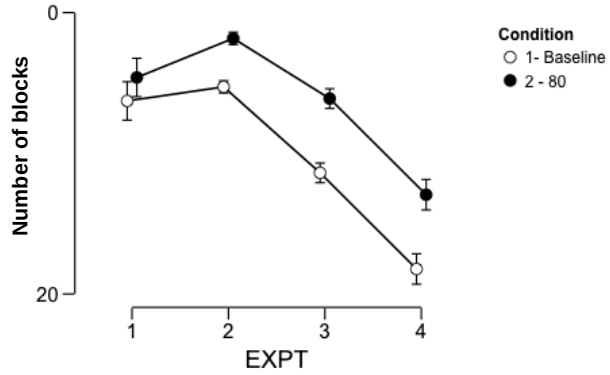


Figure 6.1.3.2. Omnibus statistics for box and blocks task

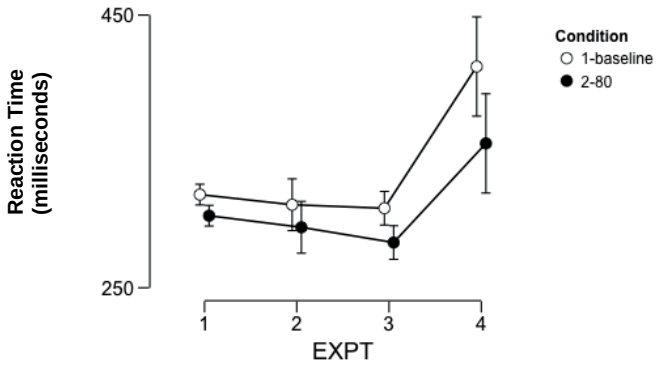


Figure 6.1.3.3. Omnibus statistics for Reaction Time Task

As I introduce in the first chapter, according to active inference, in order to initiate a movement, we must decrease the certainty in our current sensory state through attenuation of the afferent signal (H. Brown et al., 2013; K. Friston et al., 2011). It is hypothesized that reducing the synaptic gain on superficial pyramidal cells, thought to transmit bottom up prediction errors causes this attenuation and thus provides the necessary gateway to allow movement initiation to occur (Bastos et al., 2012; K. J. Friston, Bastos, Pinotsis, & Litvak, 2015). Here it was sought to artificially modulate the certainty of the proprioceptive afferent signal using high frequency peripheral vibration. Previous research has shown that peripheral vibration at 80Hz impairs performance on a number of proprioceptive tasks(Cordo et al., 1995; Inglis & Frank, 1990; Tsay et al., 2016), which is thought to be driven by increasing uncertainty in the proprioceptive input. Indeed, high frequency vibration produces the illusion that the relevant muscle is contracting in the absence of any EMG activity by transmitting incorrect kinesthetic information to the brain and spinal cord such that the brain is uncertain about the relative position of the limb (Goodwin et al., 1972; McCloskey, 1973). Moreover, previous studies have demonstrated that high frequency peripheral vibration leads to sensory attenuation, as indicated by a decrease in the amplitude of SSEPs evoked by electrical stimulation of the afferent nerve. Peripheral vibration at 60Hz causes an attenuation of early components of the cortical and cervical SSEP (Abbruzzese et al., 1980; L. G. Cohen & Starr, 1985); yet, 50 Hz cutaneous vibration between the thumb and finger and 20 Hz vibration at the wrist does not produce significant sensory attenuation (Kakigi & Jones, 1986; Legon & Staines, 2006). Here it has been demonstrated that high frequency

peripheral vibration at 80Hz, and not 20Hz, decreases reaction time and completion time on a number of behavioral tasks. Based on previous empirical and theoretical work, it was hypothesized that this is due to an increase in proprioceptive uncertainty causing an attenuation of the afferent input. However, I did not measure the magnitude of any kinesthetic illusions that may have been induced in this task therefore do not have a direct measure of proprioceptive uncertainty. Future work will be required to fully determine and characterize the causal relationship between peripheral vibration and estimates of somatosensory uncertainty.

Interestingly in the current study there was only a significant effect of vibration on behavioral performance at 80 Hz and not 20 Hz. Previous literature exploring the neurophysiological effect of peripheral vibration suggests that this is likely due to the mechanical stimulation of muscle spindles, most sensitive to high frequency stimulation around 80-120 Hz, which in turn readily activate 1a motor afferents (Roll et al., 1989). These afferent fibers provide an essential source of information about the dynamic position of the muscle necessary for optimal proprioceptive feedback. Neuroimaging studies have shown that high frequency vibration activates areas involved in sensory integration of information necessary for movement planning (Casini et al., 2006; Naito, Ehrsson, Geyer, Zilles, & Roland, 1999; Romaiguere, Anton, Roth, Casini, & Roll, 2003; L. Smith & Brouwer, 2005).

It has been suggested that vibration at high frequencies improves motor performance by increasing top-down proprioceptive feedback control, by attenuating bottom-up sensory input (in line with active inference), and

increasing the excitability of the sensorimotor cortex (Conrad, Scheidt, & Schmit, 2011). Furthermore, as previously described high frequency vibration modulates SSEP attenuation, however ischemic block of 1a motor afferents has been shown to eradicate SSEP attenuation (Abbruzzese et al., 1980). This supports the hypothesis that activating 1a motor afferents specifically may be necessary for sensory attenuation. Although it was not directly recorded from 1a afferents, it was hypothesized that the improvements in behavior seen specifically following 80 Hz vibration were due to an increased firing of 1a afferents, which modulated beta oscillatory activity over sensorimotor cortex and placed the sensorimotor system in a "ready-to-move" state. However, I am aware that there are other fiber endings within the muscle that would have been simultaneously activated, therefore the contribution of other afferent inputs cannot be ruled out. Combined microneurography and EEG studies are required to confirm the relationship between 1a afferent firing rate and sensorimotor beta oscillatory activity to support this hypothesis.

The work of this chapter highlights the potential use of high frequency vibration as a non-invasive treatment for PD patients as an adjunct to dopaminergic medication. However, more work is needed to identify the specificity of this effect to 80Hz stimulation frequency, to explore how long improvements in motor control last and to specifically investigate a clinically significant effect in this patient group before any claims of treatment efficacy can be made. The use of peripheral vibration to treat symptoms of movement disorders is not a novel concept and was first realized with Charcot's "Vibrating Chair" in 1892 (Goetz, 2009).

Following this there have been a number of studies investigating the clinical efficacy of peripheral vibration, particularly of the whole body (Arias, Chouza, Vivas, & Cudeiro, 2009; Chouza, Arias, Vinas, & Cudeiro, 2011; Ebersbach, Edler, Kaufhold, & Wissel, 2008; Haas et al., 2006; Kapur, Stebbins, & Goetz, 2012; King et al., 2009); however, the results have been inconsistent due to differences in the vibration protocol used, the muscles targeted, the behaviors being measured and the patient groups studied. In particular, there have been limited studies that have shown an improvement in behavioral performance in healthy controls following vibration, which is likely due to healthy controls performing at ceiling on the behavioral tasks used. Moreover, this work should be extended to explore the effect of vibration on freezing gait which may be more directly relevant for motor disorder patients.

Chapter 7. BUILDING NON-INVASIVE DEVICE FOR PARKINSON'S DISEASE "THE EMMA PROJECT"

7.1. Vibratory stimuli delivered by "Emma watch"

In the previous chapter, I have showed 80 Hz vibration applied on the right wrist improved the performance of motor task with the right hand in healthy subjects as well as PD patients. In particular, I have found that the participants were faster in performing motor tasks with the right hand. In the context of PD patients' clinical features, my results support the hypothesis that vibration might improve the bradykinesia of these patients, which is the typical slowness in performing voluntary movements.

At the precise time in which I was performing this experiment, I became aware of a device that had been developed by a researcher of the Microsoft UK research team. The device was created for part of a BBC programme entitled "The Big Life Fix". The Microsoft UK researcher developed a device shaped as a watch that delivered vibratory stimuli at the wrist. This was developed to ameliorate motor symptoms in one PD patient. The device took the name of this patient and it was labelled "Emma watch" (Figure 7.1.1.1.). The researcher reported a dramatic improvement of motor symptoms in this first patient. In this case, the improvement focussed on the tremor during writing and drawing tasks. The Microsoft UK team did not measure bradykinesia in this patient. Obviously, I was particularly impressed by this programme because it was in line with my research in PD. Therefore, my supervisor contacted the Microsoft UK research team to start a collaboration and to run a preliminary study of the "Emma watch".

Here, I aimed to test if a non-invasive device like a watch delivering high frequency peripheral vibration might improve the motor symptoms in PD patients. I was interested to test this hypothesis on tremor as well as bradykinesia.

7.1.1. Methods

The Emma watch

The Emma watch delivers vibration at 200 Hz through six small electromagnetic mechanical stimulators, three on each side of the wrist. The vibration was further modulated by a second frequency which was either 20 bpm (beats per minute) or 60 bpm. The modulation can be modified through a Microsoft app connected in Bluetooth mode with the device. It was not possible to modify the main frequency of vibration, which was fixed at 200 Hz.

There are several differences between the “Emma watch” and the device used in the study described in Chapter 6. The “Emma watch” was worn by the patient during the motor task, whereas the previous device was fixed on the table of the lab and it was applied on the right wrist before each motor task. The stimulated region of the upper limb was different and the timing of the vibration was completely different. The Emma watch delivered vibration on both lateral parts of the wrist in three different points of each side, while the previous device had a small globe and the medial part of the wrist was on the globe when it was stimulated. Thus, the latter involved some tendon vibration reflex, which was unlikely to be involved in the Emma watch function. Additionally, the previous device included the possibility to vary the

frequency of the vibration from 10 Hz to 100 Hz instead the Emma watch was built with the possibility to delivery only 200 Hz of vibration. However, the previous device could not modulate the frequency of vibration with a modulating frequency.

Figure 7.1.1.1. *The Emma watch delivers high frequency of vibration at 200 Hz through six small devices, three on each side of the wrist.*

Procedure and experimental design

Sixteen PD patients (5 men, 11 women, and mean age 63 years, range 52-72 years) (Table 7.1.1.1) were involved in the study. These patients were tested ON medication.

Patients	Age (y)	Gender	Disease duration (y)	UPDRS III (RUL) ON meds	Treatments
1	65	M	2	7	L+D
2	68	M	5	3	L+D
3	63	F	11	6	L
4	69	M	12	5	L+D
5	72	M	16	10	L+D
6	69	M	26	7	L+D
7	69	F	7	4	L+D
8	55	M	15	4	L
9	69	M	3	9	L
10	57	M	10	6	L
11	52	M	15	6	L+D
12	62	M	6	3	L+D
13	36	F	5	15	L
14	71	F	8	11	L
15	72	F	12	7	L+D
16	57	M	15	10	L+D
Mean $\pm$ SD	63 $\pm$ 10	F5/M11	10.5 $\pm$ 6	7 $\pm$ 3	

Abbreviations: y _ years; SD _ standard deviation; UPDRS_ Unified Parkinson's Disease Rating Scale; LD_Levodopa; D_Dopaminagonist; RUL_right upper limb.

Table 7.1.1.1. *Clinical and demographic characteristics of patients with PD.*

Idiopathic PD was diagnosed according to the UK PD Society Brain Bank criteria (A. J. Hughes et al., 1992) and further confirmed by abnormal dopamine transporter SPECT in all patients. None of the participants were on any non-PD medications that could affect the measurements performed. All participants were right-handed. Clinical disease severity was assessed with the motor section (items 3.1–3.18) of the UPDRS (Goetz et al., 2008). All patients were assessed in the ON state one hour after taking levodopa and 2 hours of taking dopamine agonists. Written informed consent was obtained from all participants. The study was approved by the local institutional ethics committee, which was the East of Scotland Research Ethics Service . Written informed consent was obtained from all participants.

The patients underwent the assessment of the motor performance of the right hand through four different tasks: 1) the nine peg hole test (Oxford Grice et al., 2003); 2) STAR tracing task; 3) SPIRAL tracing task; 4) one minute right hand tapping test with the cybernetic glove, which recorded the amplitude as well as the frequency of the tapping between the first two fingers of the right hand (Figure 7.1.1.2).

For the nine-hole peg task, subjects were instructed to place nine pegs into the nine holes as quickly as possible. The timing was recording with a stop watch (Figure 7.1.1.2.).

For the fingers tapping, the patient was instructed to perform a minute of right fingers tapping test with the cybernetic glove, which recorded the amplitude as well as the frequency of the tapping between the first two fingers of the right hand (Figure 7.1.1.2.).

The first two tests produced measures of the speed of the performance and, thus, they were our measures of bradykinesia.

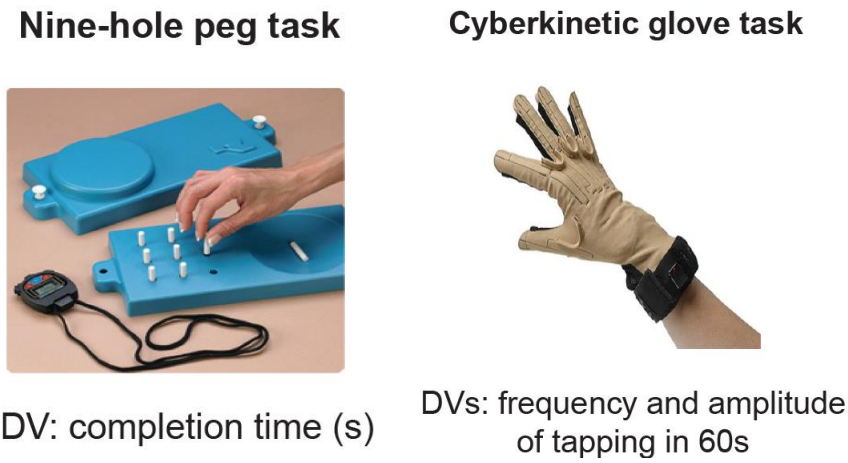
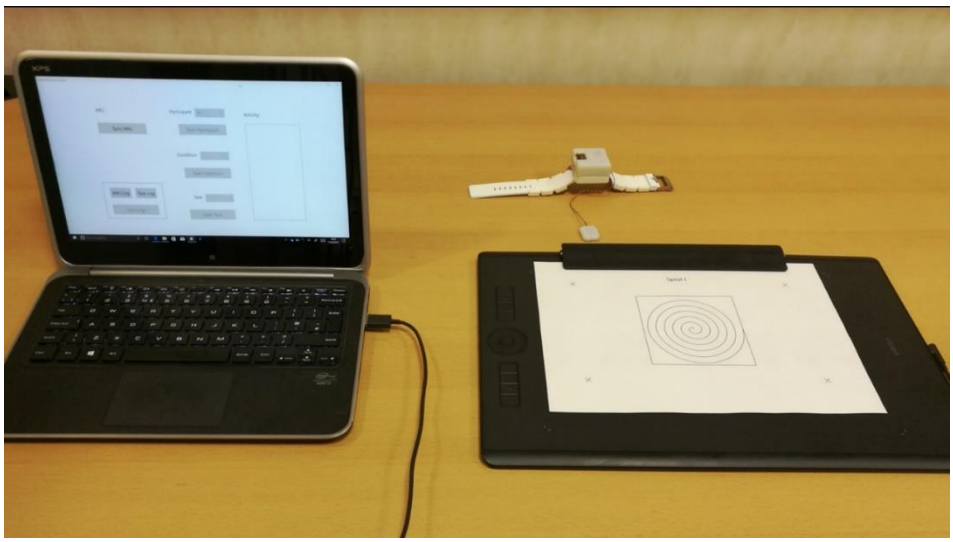


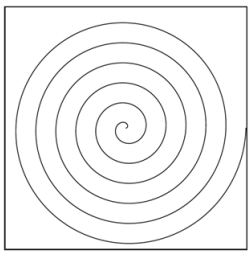
Figure 7.1.1.2. *The nine-hole peg task and the fingers tapping task were the two tests used in the study to measure the bradykinesia.*

For the STAR tracing task, subjects were instructed to trace a star as precisely and quickly as possible. The trace was on a paper which was placed on a Wacom tablet. This tablet was configured through an app built by the Microsoft UK team and connected to a laptop for recording the signals of the drawing as well as the timing to complete the task (Figure 7.1.1.3.).

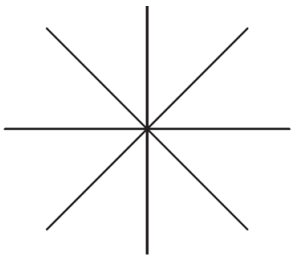
For the SPIRAL tracing task, subjects were instructed to draw a spiral in between two target lines that made the target spiral. Subjects were asked to perform this as precisely and quickly as possible. As for the STAR the subjects performed the task on the Wacom tablet (Figure 7.1.1.3.).



Drawing tests



Spiral



Star

Figure 7.1.1.3. *The paper with the trace of a spiral or a star was on the Wacom tablet and the patient was instructed to draw the spiral or the star on the trace. The Wacom tablet sent the signals of the traces on a specific app that allowed the record the drown spiral star in the computer.*

Each task was repeated in three different condition in a randomized order: 1) absence of vibratory stimuli 2) during 200 Hz vibration (+ 60 bpm modulation) on the right wrist 3) during 80 Hz vibration (+ 20 bpm modulation) on the right wrist.

Participants were given 3 attempts at each task in each condition.

Additionally, the nine peg-hole test was also performed following 30 seconds of 80 Hz vibratory stimuli on the right wrist. It was used the same device used in the study described in chapter 6. The vibratory stimuli were delivered using the device of the previous study: the electromagnetic mechanical stimulator (Ling Dynamics System) with a 3-cm-diameter circular probe under the palm wrist of the right hand. The probe was positioned orthogonally to, and under slight pressure, against the wrist of the right hand. The vibration frequency was 80Hz based on previous research showing that vibration at this frequency drives kinaesthetic illusions and thus modulates proprioceptive uncertainty (Goodwin et al., 1972; McCloskey, 1973).

The order of the tasks was randomized in each participant.

Data analysis

The following dependent variables were recorded for each motor task tested across the experiment described:

- Nine peg hole test: corrected mean completion time of the test (seconds)

- For the STAR tracing task and SPIRAL tracing task: corrected mean error of performance, which was the average of the absolute error from the target at every time point.

- Tapping test with the cyber glove: corrected mean frequency and amplitude of the tapping over 1 minute of time window.

These were the measures of movement performance in our study. We calculated the corrected mean value for each parameter. The mean corrected values removed the between subject effect by removing the mean value across conditions for each subject.

For each test a one-way repeated measure analysis of variance (rmANOVA) was conducted for each dependent variable using the following factor: condition (no vibration, vibration at 60 bpm and condition at 20 bpm). Post-hoc tests were conducted with Bonferroni corrections for multiple comparisons. P values less than 0.05 were considered to be significant. SPSS Statistics software (version 22.0.0) was used for the statistical analysis data from the blocks and box test and the nine-hole peg task. Custom code written in Matlab (version 2015a) was used to analyse the reaction time results and the frequency and amplitude of the tapping.

7.1.2. Results

As I have described in the methods section, the nine peg hole test was performed with the Emma watch but also with the device used in the study described in chapter 6. This device was used with a vibration at 80 Hz, which was the frequency that showed an improvement of the motor performance in the previous study. Interestingly, I replicated these results in this study performed by a naïve population of PD patients.

For the nine peg hole test, a repeated measures ANOVA with the condition as intra-subject factor with 4 levels (no vibration vs 200Hz vibration with 60 bpm modulation vs 200Hz vibration with 20 bpm modulation vs 80Hz vibration) revealed a significant main effect of the condition on the mean completion time of the nine-peg hole test, ($F(1, 15) = 10.168$, $p = 0.006$ $Eta^2 = 0.404$) (Fig. 7.1.2.1). Post-hoc pairwise comparisons corrected for multiple comparisons revealed a significant difference between mean completion time following 80 Hz vibration on the right wrist and no vibration ($p=0.01$, $t(15) = 3.577$). These results replicated the results of the study described in chapter 6. Furthermore, there was a significant difference between mean completion time following 200Hz vibration with 60 bpm modulation and no vibration ($p=0.04$, $t(15) = - 1.713$). Interestingly, there was no significant difference between the mean completion time following 80Hz vibration and 200Hz vibration with 60 bpm ($p=1.00$, $t (15) = 0.941$), showing that these two frequencies improved the motor performance in the similar way. Additionally, there was there was no significant difference between mean completion time following 200Hz vibration with 20 bpm modulation and no vibration, ($p = 1.00$, $t (15) = 0.427$).

For the frequency of the fingers tapping, a repeated measures ANOVA with the condition as intra-subject factor with 3 levels (no vibration vs 200Hz vibration with 60 bpm modulation vs 200Hz vibration with 20 bpm modulation) did not reveal a significant main effect of the condition on the mean completion time of the nine-peg hole test, ($F (1, 15) = 1.28$, $p = 0.29$ $Eta^2 = 0.079$) (Fig. 7.1.2.1). Post-hoc pairwise comparisons corrected for multiple comparisons did not show a significant difference between frequency of the fingers tapping following 200Hz vibration with 60 bpm and no vibration ($p=0.86$, $t(15)= -1.168$) neither between 200Hz vibration with 20 bpm and no vibration ($p=0.78$, $t(15)=1.097$).

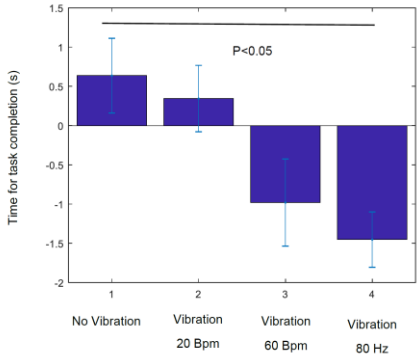
For the amplitude of the fingers tapping, a repeated measures ANOVA with the condition as intra-subject factor with 3 levels (no vibration vs 200Hz vibration with 60 bpm modulation vs 200Hz vibration with 20 bpm modulation) did not reveal a significant main effect of the condition on the amplitude of the fingers tapping, ($F (1, 15) = 1.056$, $p = 0.36$, $Eta^2 = 0.066$) (Fig. 7.1.2.1.). Post-hoc pairwise comparisons corrected for multiple comparisons did not reveal a significant difference between amplitude of the fingers tapping following 200Hz vibration with 60 bpm and no vibration ($p=1.00$, $t(15) = -0.961$) neither between 200 Hz vibration with 20 bpm and no vibration ($p=0.36$, $t(15) = -1.316$).

For the drawing star task and the drawing task, a repeated measures ANOVA with the following factors: task with two levels (star task vs spiral task) and condition with three levels (no vibration vs 200Hz vibration with 60 bpm modulation vs 200Hz vibration with 20 bpm modulation) showed a main effect of the task ($F (1,15) = 37.92$, $p= 0.000$). Indeed, there was more

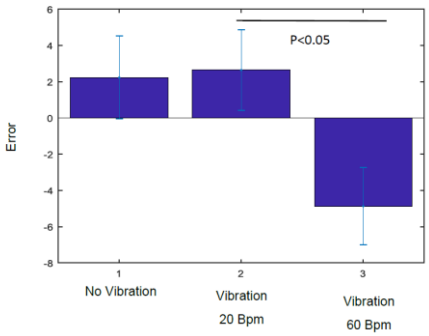
error in the spiral task than in the star task. There was no interaction between the two factors (F (1.80, 26.93) = 0.454, p= 0.61).

A repeated measures ANOVA with the following factors: task with two levels (star task vs spiral task) and condition with two levels (200Hz vibration with 60 bpm modulation vs 200Hz vibration with 20 bpm modulation) showed a main effect of main effect of the task (F (1,15) = 46.72, p= 0.000). Notably, there was a main effect of the condition (F(1.15)=6.40, p=0.02). There was no interaction between the two factors (F (1, 15) = 0.525, p= 0.48). Thus, there was the same modulation in both tasks.

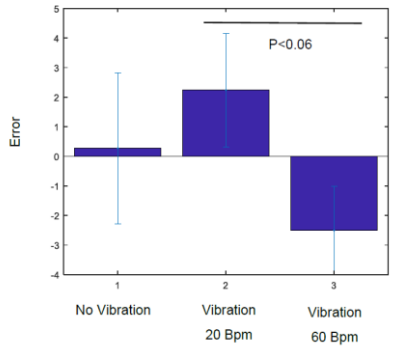
Performance on the drawing 9 Peg Hole task



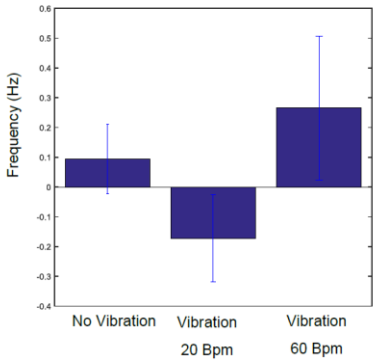
Performance on the drawing STAR task



Performance on the drawing a SPIRAL task



Frequency of the fingers tapping



Amplitude of the fingers tapping

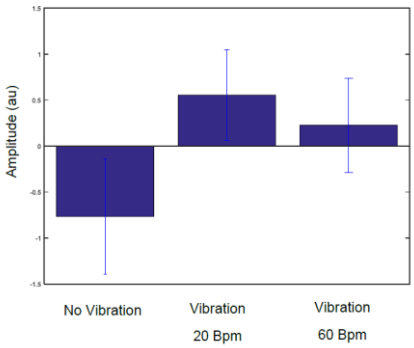


Figure 7.1.2.1. *Results of the tasks performed by PD patients ON medications. Note if there was no modulation then each condition would be centered on zero in each bar graph.*

7.1.3. Discussion

The current study aimed to test non-invasive devices to improve motor signs of PD. The results of this study are interesting because the mechanism of action of the “Emma watch” is hypothesized to be different compared the device used in the previous study. Indeed, as it has been previously discussed the previous device was supposed to use the TVR and the spindle mechanism.

The Emma watch is really not likely to be stimulating the spindles. Indeed, I hypothesized that it is likely that this device uses the cutaneous stimulation although I have no really direct neurophysiological data to support this. Here, a peripheral vibrating stimulus at 200 Hz was used to change the tactile signal. The 200 Hz was tested with two different modulation: 60 bpm and 20 bpm. I found that 200 Hz peripheral vibration at 60 bpm modulation applied to the right wrist during the performance of different tasks of a total of 16 PD ON medication. There was an improvement of performance related to movement speed as well as precision of tasks on a number of motor control tasks, especially the nine peg hole test and the drawing tasks. In contrast, peripheral vibration at 200Hz with 20 bpm had no effect on motor performance. There was not a clear improvement regarding the fingers tapping with 60 bpm modulation.

Overall, it is clear that peripheral vibration at 200 Hz at 60 bpm improved motor performance on a variety of motor tasks.

The main results are that high frequency peripheral vibration at 200 Hz with 60 bpm, and not 20 bpm, decreases completion time on nine peg hole task and improve the precision of drawing tasks.

These results open the interesting scenario to test the vibro-tactile stimulation in PD and to test the potential mechanism underlying this improvement.

The other major interesting characteristic of the Emma watch compared to the previous electromagnetic vibratory stimulator was the possibility of modulating the frequency of the vibration. Here I demonstrated the Emma watch was only effective at improving motor performance when the 200 Hz vibration was modulated at 60 bpm. It is important to stress that the modulating frequencies employed here chosen not based on some previous literature but because they had previously worked on the one pilot subject that was part of the BBC television program. Why 60 bpm modulating frequency improves motor performance remains an outstanding interesting question and I can only speculate as to why 60 bpm leads to improved motor performance.

The work here highlights the potential use of high frequency vibration as a non-invasive treatment for PD patients as an adjunct to dopaminergic medication. However, more work is needed to identify the specificity of this effect to 200Hz stimulation frequency with 60 bpm modulation, to explore how long improvements in motor control last and to specifically investigate a clinically significant effect in this patient group before any claims of treatment efficacy can be made.

In conclusion, these preliminary data are consistent with a novel and exciting hypothesis to explain that vibrotactile stimulation at 200 Hz with 60 bpm modulating results in less slowing and (decrement in amplitude of a repetitive hand movement and less tremor) compared to baseline measures. Further work is required now to establish this finding and investigate further.

Chapter 8. VIBRATORY STIMULY AND FREEZING OF GAIT: A PRELIMINARY CASE STUDY

8.1. Insoles shoes generating vibration

In the previous chapters, I found that vibratory stimulation produced an improvement of the motor performance on the upper limb where vibration was applied. The studies focused on patients with PD. Therefore, as a neurologist specialized in movement disorders, I started to think about whether vibratory stimulation could improve other neurological signs of PD not only bradykinesia of the upper limbs. In particular, those symptoms that are particularly resistant to commonly used therapies. Naturally, my first thought was about FOG which is one of the most debilitating symptoms of PD. It is defined as 'brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk'(Nutt et al., 2011).

It is one of the most debilitating consequences of PD as it interferes with the patient's ability to move and, obviously, increases the likelihood of serious falls. Furthermore, it is one of the symptoms that does not show a significant improvement with current treatments used in these patients (levodopa/dopaminagonist and deep brain stimulation). During the time that I was thinking about the development of a vibratory device to help improve gait, Prof. Limousin was contacted by Dr Lise Pape, the funder of "Walk With Path", which is a healthcare company focused on injury prevention, improved mobility and user-centred design and intervention. Dr Pape was developing a non-invasive treatment, Path Feel insole, as a device that can improve functional walking ability and FOG via haptic feedback. The Path Feel insoles are insoles generating vibration during walking or standing.

Here the aim was to develop a pilot study to test whether vibratory noise applied to the sole of the foot could significantly reduce freezing of gait. I used Path Feel model 310 113, which delivered vibration at a frequency of 200 hz +/- 40 Hz and an amplitude of 1.4G (G-force= 1 G is equal to the acceleration from gravity:1G=9.8 m/s^2). Furthermore, the a secondary of this study aim was to determine whether the therapeutic effect would endure during the course of a week therapy and if it would remain after a week without soles.

Following this there have been a number of studies investigating the clinical efficacy of peripheral vibration, particularly of the whole body. Lipsitz et al. (Lipsitz et al., 2015) used shoes insole delivering subsensory vibratory noise to improve balance and gait in healthy elderly people.

8.1.1. Methods

A male patient with idiopathic PD (age 66 years) participated in this experiment. Idiopathic PD was diagnosed according to the UK PD Society Brain Bank criteria (A. J. Hughes et al., 1992) and further confirmed by abnormal dopamine transporter SPECT in all patients. The patient was assessed in the OFF state, 24 hours after the last dose of dopaminergic treatment, and in ON state, one hour after taking levodopa. Written informed consent was obtained from the participant and the study was approved by the local ethical committee.

Clinical disease severity was assessed with the motor section (items 3.1–3.18) of the UPDRS (Goetz et al., 2008). The clinical severity of the gait and balance impairment was assessed by the gait and balance scale

(GABS) (Thomas et al., 2004). Furthermore, the gait and falls questionnaire (GFQ) was administered to specifically assess the FOG (Giladi et al., 2000).

The activities-specific balance confidence (ABC) questionnaire was administered to measure the patient's confidence in his ability to perform daily activities without falling (Powell & Myers, 1995). The avoidance behavior due to a fear of falling was quantified with the Fear of Falling Avoidance-Behavior Questionnaire (FFABQ) (Landers, Durand, Powell, Dibble, & Young, 2011).

The patient underwent three clinical sessions. The first clinical session was before the intervention with soles and was the baseline message. In other words, the patient was naïve and it was assessed with UPDRS, GABS, GFQ, ABC and FFABQ in the following three conditions: OFF state, OFF state wearing the insoles, ON state wearing the insoles.

The second clinical session was performed after a week of wearing the insoles with the same five clinical protocols in the following three conditions: OFF state wearing the insoles, ON state wearing the insoles and ON state (without wearing the insoles).

Finally, the third session was performed after a week without wearing the insoles. The patient did not agree to come the third time to the NHNN. Therefore, I assessed him remotely just with the three questionnaires (GFQ, ABC and FFABQ).

Additionally, the patient was asked to complete a diary with the following information: number of falls, number of freezing episodes during OFF periods, duration of each freezing episode in OFF periods, number of

freezing episodes during ON periods, duration of each freezing episode in ON periods. The patient completed this diary three times: 1) during the week before the first clinical session, 2) during the week after the first clinical session in which he was wearing the insoles during his normal daily life, 3) during the week after the second clinical session in which he was not wearing the insoles.

8.1.2. Results

The participant of this study was a 66 years old man with a diagnosis of Parkinson's disease from 2007. He was treated with bilateral STN-DBS. He was on levodopa and dopaminagonists. The DBS was always ON during the assessment.

The main clinical issue for the patient was the gait disturbance with shuffling and freezing of gait. Furthermore, the patient had postural instability.

Diary

During the week before wearing the insoles, the patient did not report falls. The number of freezing episodes during OFF periods was on average once a day (7 episodes in total) and the duration of each episode was on average 30 seconds.

The patient reported only 3 freezing episodes during ON periods over that week. He had 2 episodes in one day and 1 episode another day. The rest of the week was free from these episodes. Each episode lasted on average 30 seconds. The patient reported some episodes of walking backward in average once a day during that week.

During the week with the insoles**,** the patient did not report any falls. The number of freezing episodes during OFF periods was on average 1.4 (8 in total). Interestingly, the duration was much shorter. Indeed, each episode lasted on average 2-3 seconds. There were 9 episodes of freezing during ON periods, which were mainly concentrated in two days of the week. Each episode lasted on average 1-2 seconds. Thus, there were an improvement in the duration of the freezing episodes with the vibratory insoles In addition, the patient's family reported the patient was lifting the feet more than usual during walking.

The following week (without wearing the insoles) the patient did not have any falls. Interestingly, he had only 3 episodes of freezing of gate during OFF periods, which were concentrated in two days. Interestingly, the duration of these episodes was less than a second during this week. There were less episodes of freezing during ON periods (5 in total) during this week and the duration was less than a second for each episode.

Unified Parkinson's Disease Rating Scale – part 3

The UPDRS part III was assessed during the first two clinical sessions and in the three described conditions in each session. During the first clinical session (baseline), the UPDRS part III score in OFF state was 40. The score was 37 in OFF state wearing the insoles and 15 in ON state wearing the insoles (Figure 8.1.2.1).

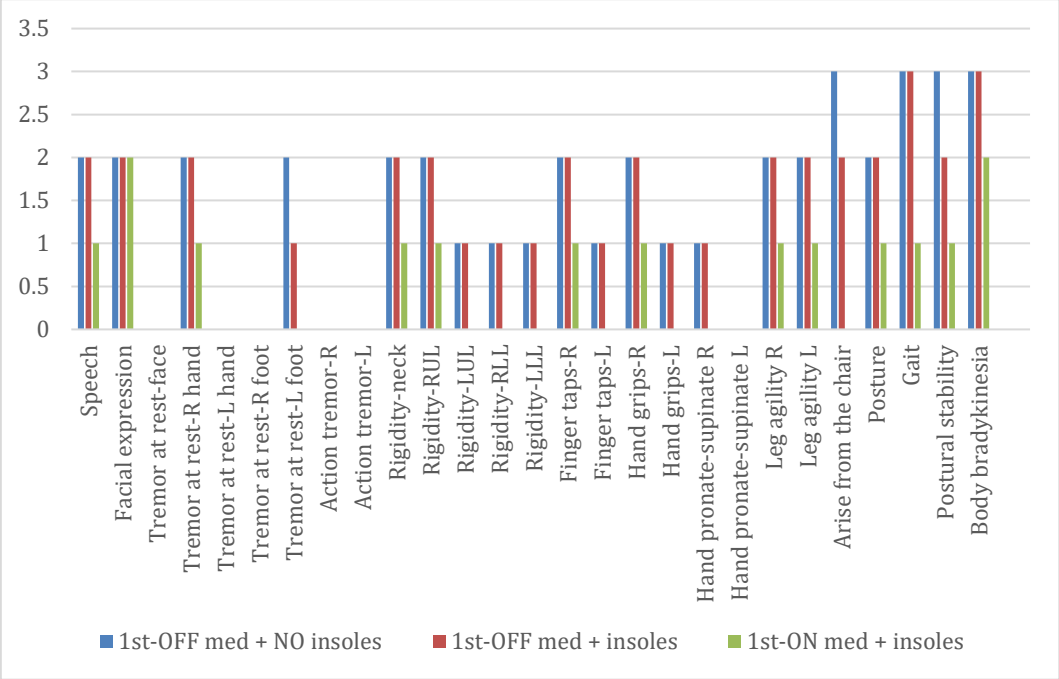


Figure 8.1.2.1. *Score of the individual items of UPDRS part III during the first clinical session in the three described conditions.*

The UPDRS part III was recorded after a week wearing the insoles at the second clinical session. The score was 34 in OFF state wearing the insoles, 12 in ON state wearing the insoles as well as in ON state without wearing the insoles (Figure 8.1.2.2).

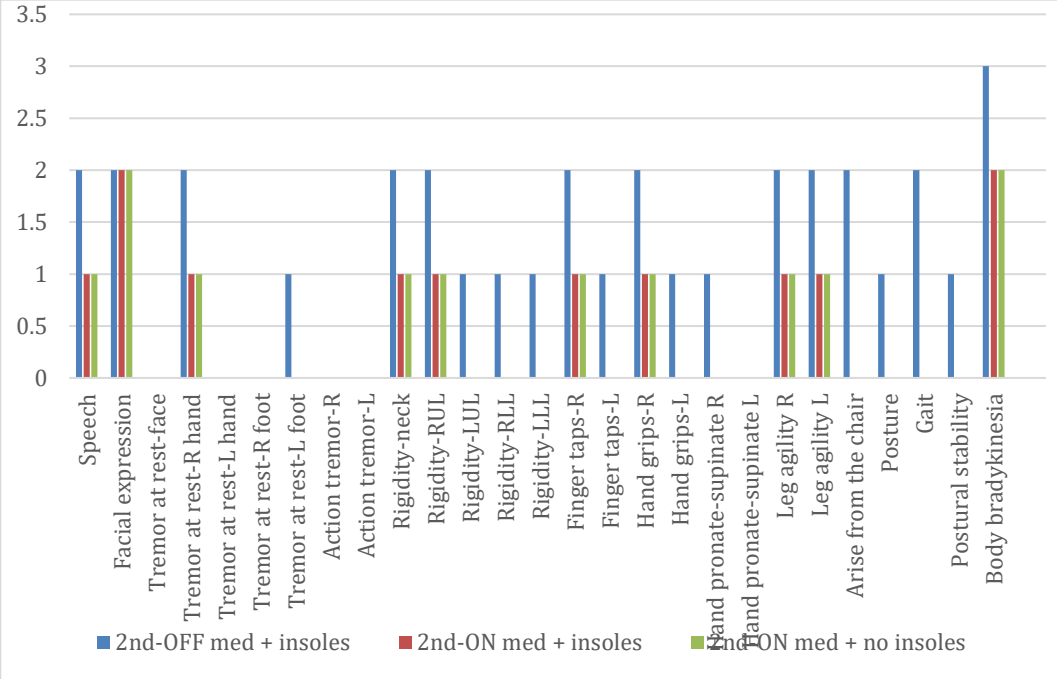


Figure 8.1.2.2. *Score of the individual items of UPDRS part III during the first clinical session in the three described conditions.*

Gait and balance scale (GABS)

The part A.1 of GABS includes the historical information of the patient. Therefore, it was administered just once at the beginning of the study. The total score of the GABS was 9 (Figure 8.1.2.3).These results showed the presence of significant FOG in this patient.

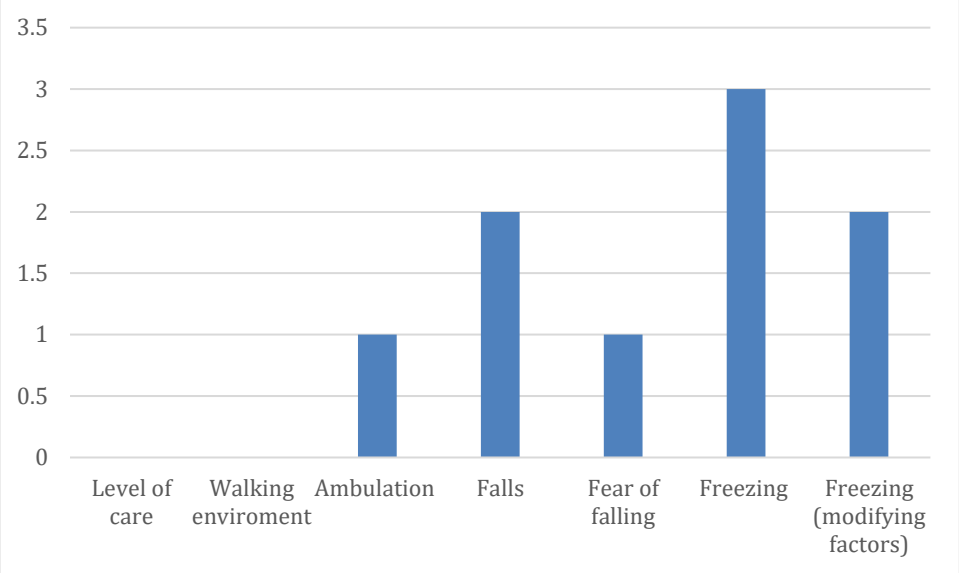


Figure 8.1.2.3. *Score of the individual items of GABS part A.1*

The part B.1 of GABS includes the physical examination of the patient at it was performed in the first two clinical sessions. At the baseline (first clinical session), the total score was 52 in OFF state, 44 in OFF state wearing the insoles and 26 in ON state wearing the insoles (Figure 8.1.2.4).

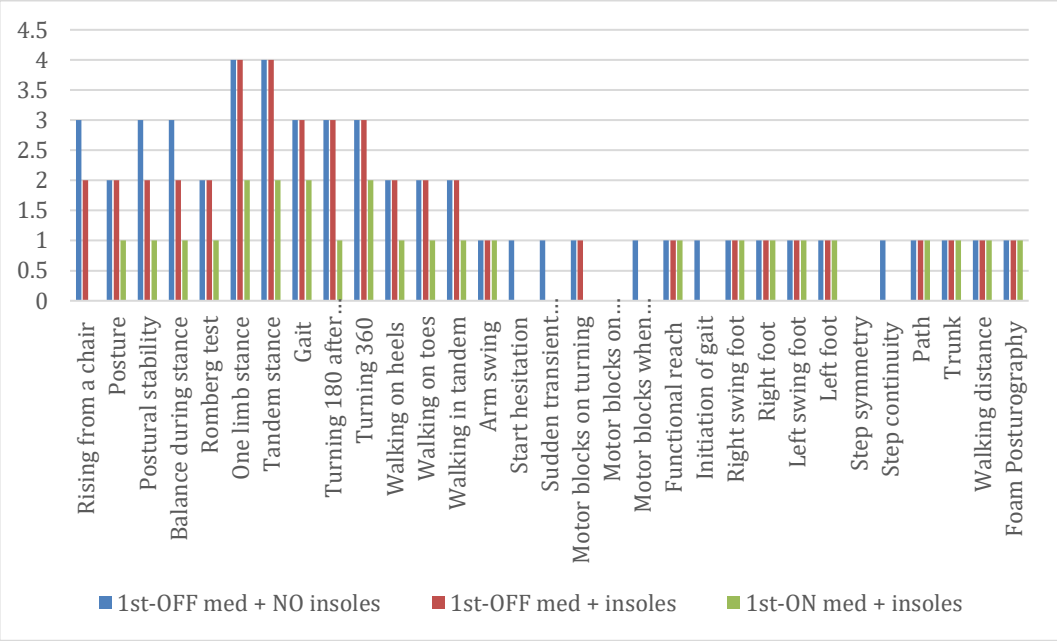


Figure 8.1.2.4. *Score of the individual items of GABS during the first clinical session in the three described conditions.*

The GABS total score after a week wearing the insoles (second session) was 39 in OFF state wearing the insoles, 14 in ON state wearing the insoles as well as without the insoles (Figure 8.1.2.5).

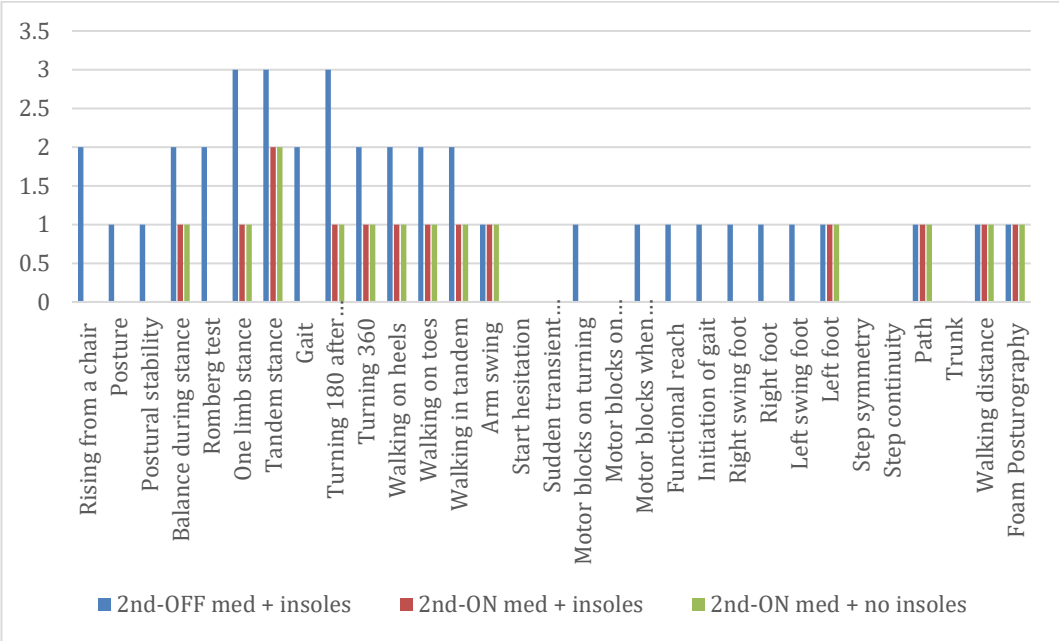


Figure 8.1.2.5. *Score of the individual items of GABS during the second clinical session in the three described conditions.*

The part B 2 of GABS includes the following three timed tasks: timed walking at usual speed (5 m; measures: time in seconds, number of steps, cadence [number of steps per min with the subject walking at a normal speed, steps/min]), timed walking as fast as possible (5 m, measure: time in seconds) and the stand–walk–sit time (total 10 m as rising from a chair and walking 5 m, turn 180 degrees, walk back and sit down, measure: time in seconds).

At the baseline (first session), the timed walking at usual speed was 30 seconds with 15 steps and cadence of 30 steps/min in OFF state. It was 25 seconds with 10 steps and cadence of 25 steps/min in OFF state wearing the insoles. It was 20 seconds with 7 steps and cadence of 21 steps/min in ON state wearing the insoles. The timed walking as fast as possible was 20 seconds in OFF state, 15 seconds in OFF state wearing the insoles and 10 seconds in ON state wearing the insoles. The stand–walk–sit time was 60 seconds in OFF state, 50 seconds in OFF state wearing the insoles and 30 seconds in ON.

After wearing the insoles for a week (second session), the timed walking at usual speed was 25 seconds with 10 steps and cadence of 25 steps/min in OFF state wearing insoles. It was 15 seconds with 8 steps and cadence of 32 steps/min in ON state wearing the insoles as well as in ON state without wearing the insoles. The timed walking as fast as possible was 15 seconds in OFF state wearing insoles, 10 seconds in ON state wearing the insoles and 15 seconds in ON state without insoles. The stand–walk–sit time was 50 seconds in OFF state wearing the insoles, 25 seconds in ON state wearing the insoles as well as in ON state without insoles.

Activities-specific balance confidence (ABC) questionnaire

The ABC questionnaire was performed once during each clinical session. The first part of the ABC questionnaire tests how confident the participant feels himself to perform 10 listed activities without falling. The subject has to give a score from 1 (extreme confidence) to 10 (absence of confidence) to each activity.

The ABC part 1 total score was 46 at baseline, 29 after a week wearing insoles and 20 the following week (without insoles) (Figure 8.1.2.6)

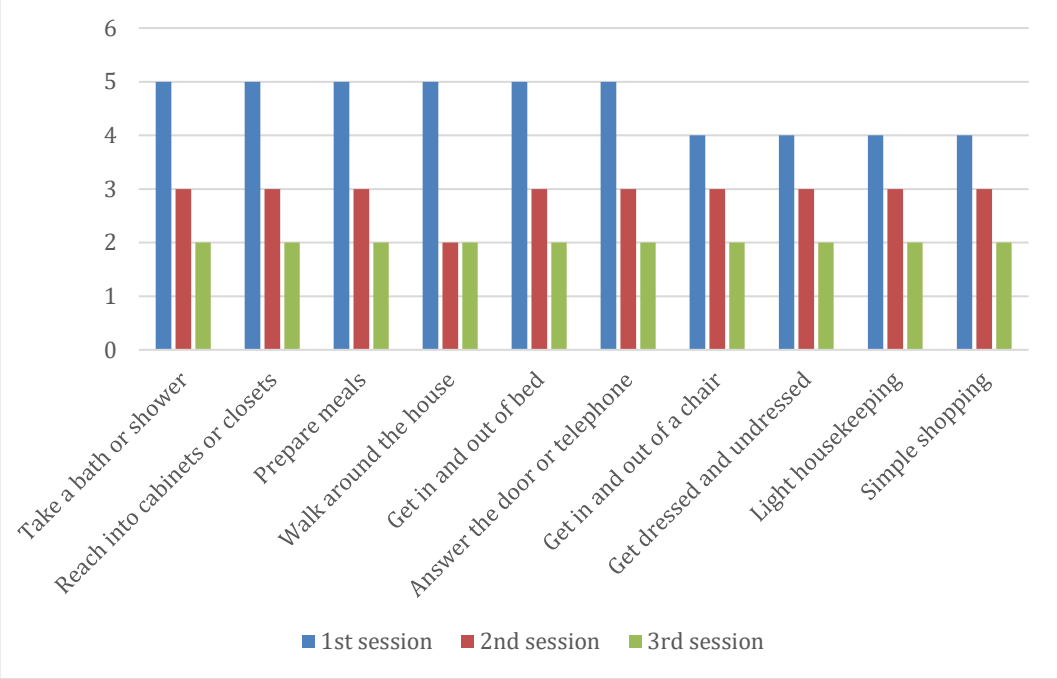


Figure 8.1.2.6. *Score of the individual items of ABC part 1 during each condition.*

The second part of the ABC questionnaire tests the level of self-confidence in not losing the balance or becoming unsteady during 16 listed activities. The subject has to give a score from 0% (no confidence) to 100% (completely confident) to each activity.

I have indicated the individual score for each activity in the figure 8.1.2.7.

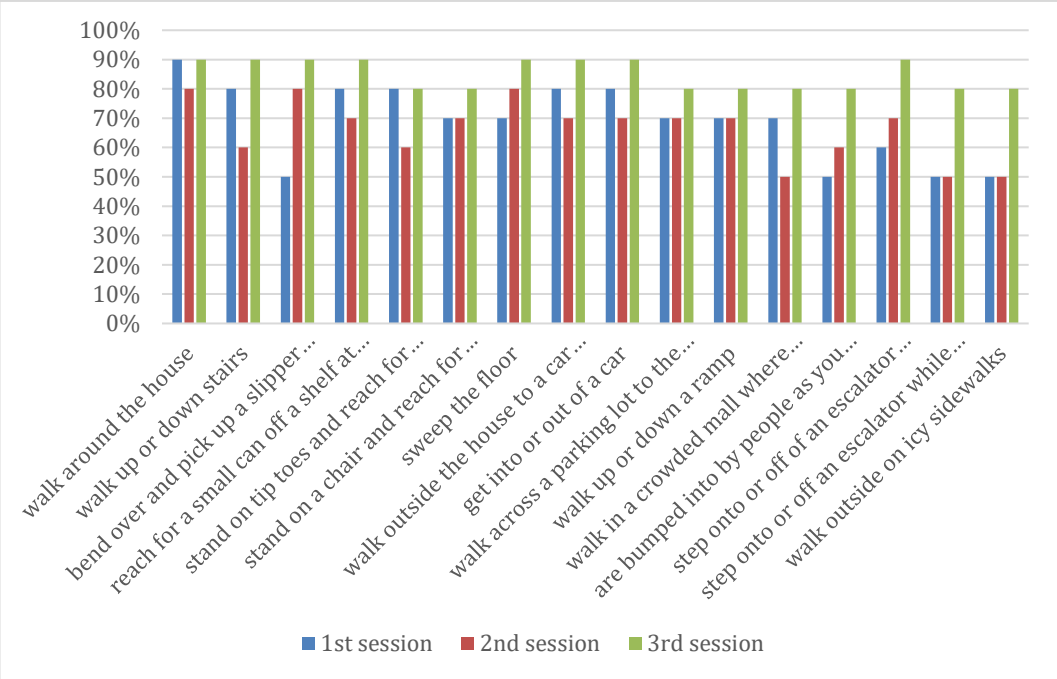


Figure 8.1.2.7. *Score of the individual items of ABC part 2 during each session.*

Fear of Falling Avoidance-Behavior Questionnaire (FFABQ)

The FFABQ tested the fear of falling through avoiding behaviors related to 16 listed activities. The participant had to give a score from 1 (completely disagree) to 5 (completely agree) for each question asking “due to my fear of falling, I avoid ….”. I have indicated the individual score for each activity in the figure 8.1.2.8.

Interestingly, during the week wearing the insoles the patient had several avoiding behaviours related to the fear of falling (higher score in each item compared to the other two sessions). This might be related with the feeling of vibration, which is a new feeling for the patient, and it might cause a reduced confidence. On the contrary the fear of falling was reduced in the main numbers of item during the third session and the results were equal to the first week (baseline) apart from 3 items: going up and downstairs, walking in crowded places, work/volunteer work. These three activities were associated with lower fear of falling and, thus, lower avoiding behaviour during the third week of the study. These results suggested that there was some long-term improvement, which was not evident during wearing the insoles.

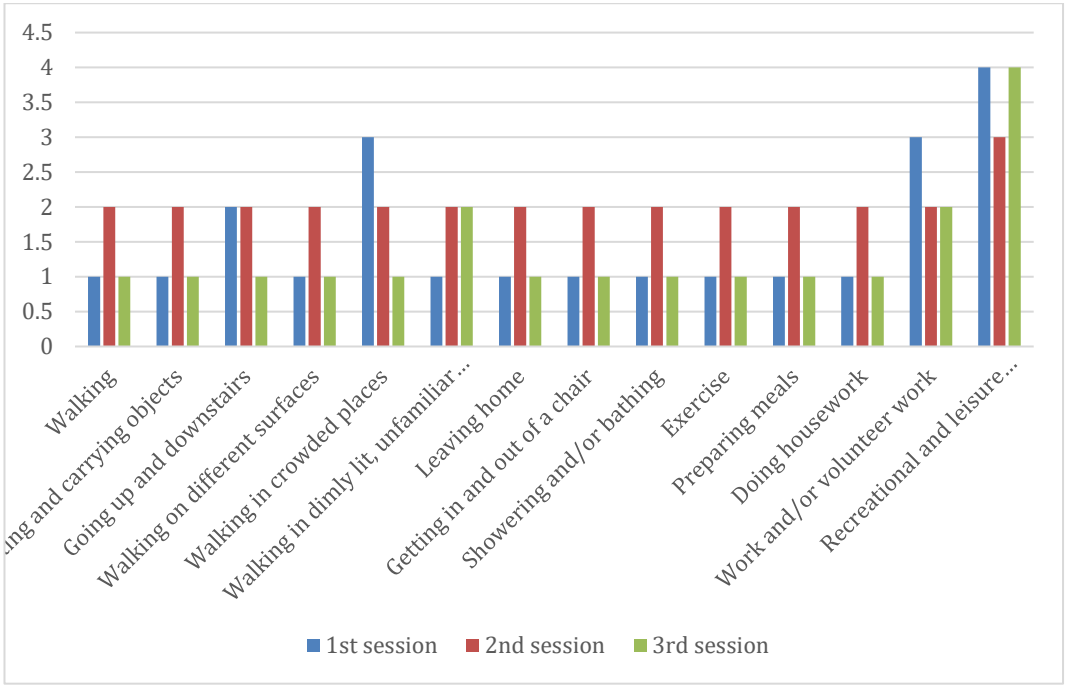


Figure 8.1.2.8 *Score of the individual items of FFABQ during each session.*

Gait and falls questionnaire (GFQ)

The part A of the GFQ questionnaire tests 16 different issues related to gait, balance and FOG and the participant had to give a score from 1 (absence of the impairment) to 4 (severe impairment). I have indicated the individual score for each activity in the figure 8.1.2.9. It is clear from the graph that there was an improvement during the third week of the study in the gait (especially the duration of the gait).

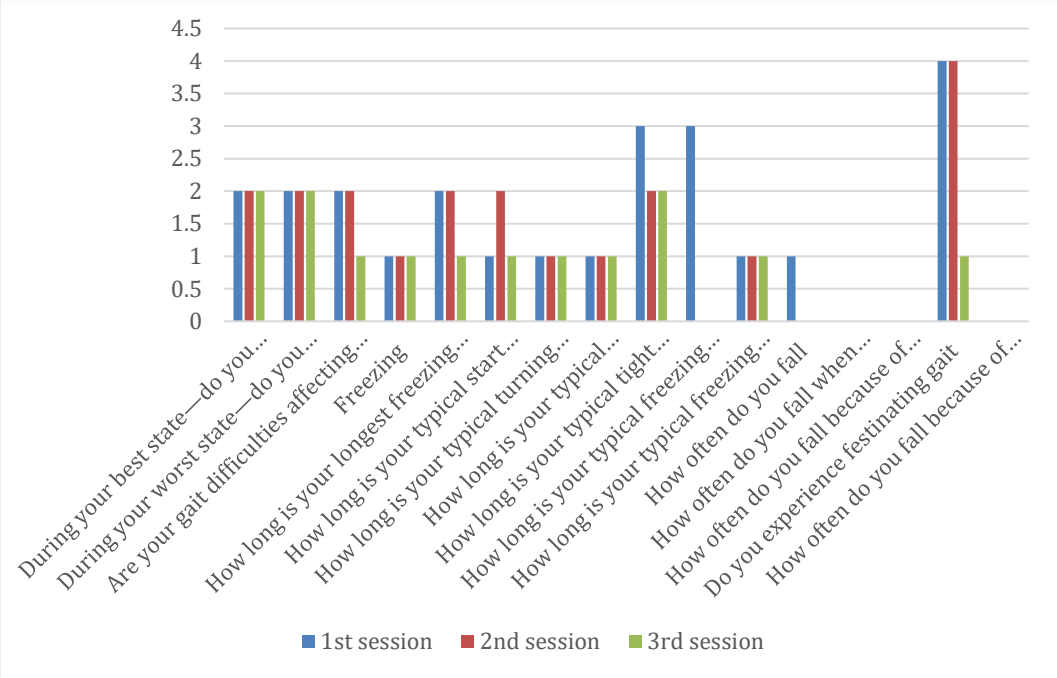


Figure 8.1.2.9 *Score of the individual items of GFQ part A during each session.*

The part B of GFQ questionnaire tests 6 different aspects of FOG and the participant had to give a score from 1 (absence of the impairment) to 4 (severe impairment). I have indicated the individual score for each activity in the figure 8.1.2.10. Notably, the FOG showed a clear improvement during the third week of the study. There were not significant improvements reported during the second week, the week wearing the insoles.

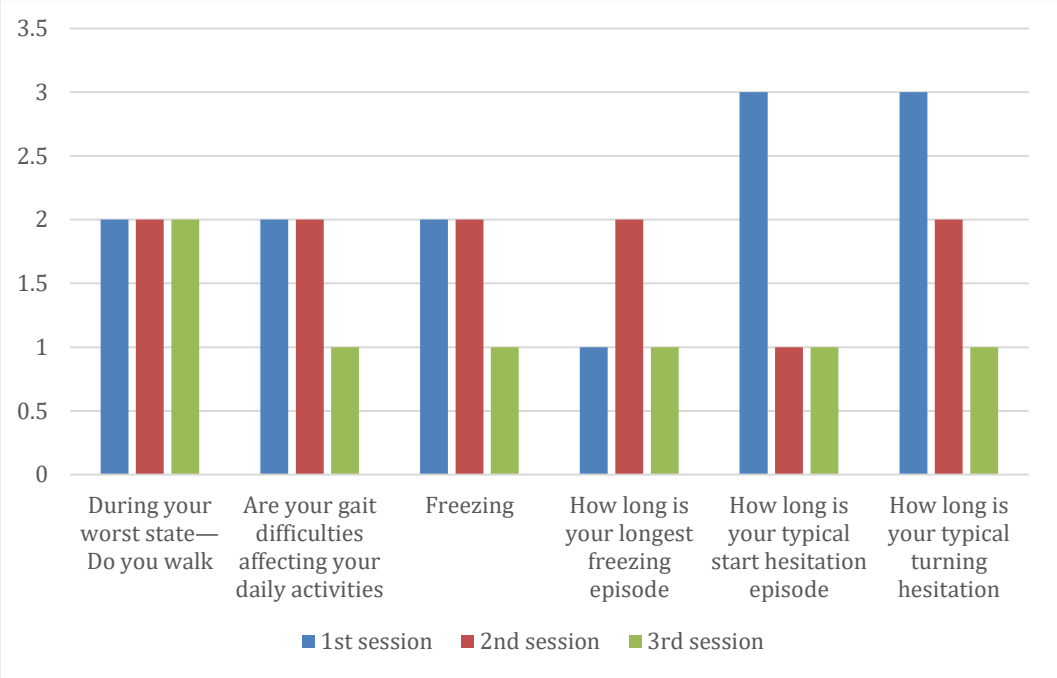


Figure 8.1.2.10 *Score of the individual items of GFQ part B during each session.*

8.1.3. Discussion

The aim of the current study was to test the efficacy of a non-invasive device generating vibratory stimulation, labelled Path Feel, to improve FOG. Path Feel delivers vibration with frequency at 200 Hz +/- 40 Hz and amplitude of 1.4G.

The Path Feel insoles appeared to have been well received by the participant of this study, who had been diagnosed with PD and who was affected by severe FOG. Participant feedback was positive towards the product and clinical improvements were measured. Indeed, several scores showed an improvement over the 3 sessions implying that Path Feel did improve the freezing of gait in this patient.

Interestingly, the patient's diary showed an improvement of the FOG episodes during the week with the insoles compared to the baseline. Indeed, although there was not a reduction in the number of episodes, the duration of each episode was considerably shorter during the week with the insoles (1-3 seconds) compared to the baseline (30 seconds). Shorter FOG episodes reduced the probability of falling because they interfere less with balance. The most interesting data was that the number of FOG episodes. This was dramatically reduced during the following week compared to the previous week with the insoles. Indeed, the average number was reduced from 8 to 3 during OFF state and from 9 to 5 during ON state. Additionally, the duration was shorter (from 3 seconds to <1 second).

The subjective information from the patient were confirmed by the clinical score recorded by the clinical researcher. Indeed, the UPDRS part III

showed an improvement after a week wearing the insoles compared to the baseline. Indeed, it was reduced from 37 in OFF state and from 15 to 12 in ON state. Obviously, the reduction was recorded in the items related to gait and posture functions.

The scores of GABS part B1 were in line with the previous data. Indeed, the total score showed a reduction from 44 in OFF state wearing the insoles at baseline to 39 in the same state after a week wearing the insoles. The reduction was from 26 in ON state wearing the insoles at baseline to 14 in same state at the second session. The improvement was particularly evident in the items related to motor blocks, gait initiations, hesitations and posture.

The three timed tasks of part B2 of GABS showed a faster walking in all tasks after a week wearing the insoles compared the baseline and the improvement was in both states: OFF wearing the insoles and ON wearing the insoles.

Interestingly, the first part of ABC, which tested the confidence of the patient to perform some activities without falling showed a progressive reduction over the three clinical sessions (46 vs 29 vs 20). Lower scores are related to higher confidence without falling. The most interest aspect of these results is that the lower score was recorded at the third clinical session, thus, after the second week, which was the one without wearing the insoles but after a week wearing the insoles.

The second part of the ABC showed complementary results to the first part. Indeed, this section tested the level of self-confidence in not losing the

balance during 16 daily activity. There is not a total score but a percentage score for each item. Here, higher percentage scores are related to higher confidence without losing balance. As it is showed in the figure 8.1.2.7, the higher scores are registered in each item during the third clinical session confirming that the patient reported more confidence in his balance in the week after the one wearing the insoles as a long term benefit from vibratory stimulation.

The FFABQ tested the fear of falling which leads to avoiding some activities. The higher score (5) means that the patient avoids to perform some tasks due to the fear of falling. Interestingly, the lower score in each item was registered during the third clinical session. However, the higher score in each item was registered during the first week, during wearing the insoles. These data might suggest that vibratory stimulation has a positive impact on the balance after it is applied but has a negative impact on the balance during the application. It is likely that the vibration under the feet when the patient is standing help to break the FOG loop but give a feeling of unsteadiness to the participant.

In line with the FFABQ's data were the GFQ part A as well as part B. Indeed, more impairment in each activity related to gait, balance and FOG was recorded at the second session with similar results to the first session, whereas lower scores (reduced impairment) was showed at the third session (figure 8.1.2.9 and figure 8.1.2.10).

In conclusion, there was a coherent improvement of all score during the 3rd week of the study which was the week following the one with the insoles.

This result suggests that the benefit of the vibratory stimulation on the FOG is not immediate but it is evident after an interval of time.

Increasing the size of the data set is mandatory. A possible recommendation for future direction would be to conduct long-term studies with an appropriate cohort.

Chapter 9. GENERAL CONCLUSIONS AND FUTURE STUDIES

The general aim of the work proposed in this thesis was to test a novel theoretical account of movement and movement disorders. Specifically the aim was to test whether this account can explain some of the hypokinetic symptoms observed in PD. The aim was to combine experimental and theoretical research to test predictions of the active inference framework, specifically to test whether a failure of sensory attenuation can explain the hypokinetic movement disorders of PD. Furthermore, the thesis aims to explore the possibility to improve motor signs of PD by artificially modulating the uncertainty in the proprioceptive signal through vibration.

In the following sections, I will discuss the individual aims tested during my PhD.

Sensory attenuation

I studied the phenomenon of SA in two different axes. I firstly characterized SA at the onset of voluntary movement in a cohort of normal subjects. I secondly characterized this phenomenon in a cohort of PD patients and I tested the hypothesis that this phenomenon might be modulated by dopaminergic treatment. I presented data on SA which was tested in normal subjects and in PD in ON and OFF. The results demonstrated that SA was significantly reduced in PD OFF medication. SA is the top-down filtering of this afferent information to limit how much feedback is received. It has been proposed that the role of this sensory gating is to differentiate between sensations created by one's own movements and those created from

external stimuli to highlight the biologically more salient and less predictable external sensory input (Wolpert et al., 1995; Wolpert and Miall, 1996; Shergill et al., 2005). An alternative hypothesis posits that SA is a necessary preparatory step to allow movement initiation to occur (Brown et al., 2013). This last hypothesis has been tested in my PhD. The prediction was that PD patients who have a deficit in movement initiation should consequentially have a deficit in SA. This hypothesis has been confirmed by both the studies in chapter 4 and 5. My results demonstrate that PD is characterized by abnormal SA. Furthermore, in both studies, I showed that dopaminergic treatments modulate SA and they normalize SA in the PD ON state. Indeed, I did not show any significant differences between age matched healthy controls and PD ON medication in terms of SA. Importantly, I replicated this result in two different populations of patients and age-matched healthy controls. This result is of interest as bradykinesia is one of the cardinal signs of PD and it has the best response to dopaminergic treatments. My results provide evidence that the severity of bradykinesia might be associated with a failure in SA. This potentially opens up new avenues of research into bradykinetic symptoms of PD and provides evidence for a new mechanistic of account of these symptoms, linking them to sensory gating.

In Chapter 4 I measured SA in a cohort of healthy participants and explored its relationship with voluntary movement monitored through EMG recording in the active muscles. I found strong evidence of presence of SA at the onset of movement in the healthy subjects. I found normal SA in PD in ON pharmacological state. Interestingly the analysis of the SA in PD patients in OFF pharmacological state showed reduced SA at the onset of the performed voluntary movement (thumb abduction). This finding firstly

provides evidence that SA is modulated by the dopaminergic treatment at the onset of movement and secondly suggests that the reduced SA might be the physiological mechanism underlying the deficit in the movement initiation in this group of patients.

I have studied the SA in the physiological field. Indeed, my measure of SA is the amplitude of SSEPs. It is well known that SA has been extensively studied also in the perceptual field. In this regard, it has been suggested that “movement-induced somatosensory gating may be the physiological correlate of the decreased sensation associated with self-produced tactile stimuli in humans”(Blakemore, Wolpert, & Frith, 2000). Perceptual SA has been described as a reduction in the perception of the afferent input of a self-produced tactile sensation and is referred to as the inability to tickle oneself. This has been attributed to a central cancellation of the reafferent sensory signal by the efference of the motor signal before making the tickling action. When someone else is producing the tickling sensation, there is no efference copy to cancel out or reduce the incoming afference, so the sensory information is not attenuated (Blakemore et al., 2000; Blakemore et al., 1998). The perceptual SA has been proposed to have the role to help humans to distinguish between self-generated and externally generated sensations. It has been suggested that perceptual attenuation may be driven by activity in the secondary somatosensory cortex (Blakemore et al., 1998; Shergill et al., 2003), whereas SSEP attenuation is driven by activity in SI. Indeed, early SSEP components that are attenuated during movement originate from activity in SI (G. Hughes, Desantis, & Waszak, 2013).

To the best of my knowledge, Palmer et al. have been the first researchers that have tested the potential correlation between physiological as well as perceptual SA. These authors measured SSEP elicited by median nerve stimulation during a force-matching paradigm. To measure perceptual sensory attenuation, a classic force-matching task was used (Parees et al., 2014; Shergill et al., 2003). Subjects received a force (produced by robot 1) on their left index finger for 3 s. They were instructed to match the intensity of that force on the same finger by either pushing down on robot 1 to emulate the force produced ("self" condition) or by pushing down on robot 2. Robot 2 was linearly connected to robot 1 such that a 1 cm movement in robot 2 produced a 1.25 N downward force on robot 1. Once the subjects had produced the appropriate force, they were instructed to hold the matched force until they heard the stop signal (4.5 s). The intertrial interval was 1 s (C. E. Palmer, Davare, & Kilner, 2016). Median nerve stimulation (MNS) was either given while holding the matched force only or additionally during force production. Subjects completed alternate blocks of each condition counterbalanced across participants.

Interestingly, the authors showed that these two forms of SA have dissociable neurophysiological correlates and are likely functionally distinct. My results together to Palmer's results have important implications for understanding neurological disorders in which one form of SA but not the other is impaired. The important implications of these studies are that some neurological disorders as PD are characterized by an abnormal physiological SA but they might have normal perceptual SA. Therefore, the next step should test the perceptual SA in PD to test if this hypothesis is correct. Previous studies have investigated whether there are abnormal

physiological SA (Macerollo et al., 2016) and perceptual SA (Parees et al., 2014) in other movement disorders, namely functional movement disorders. Both studies found that patients with functional movement disorders showed reduced physiological as well as perceptual SA.

Identifying how deficits in physiological and perceptual sensory gating interact and why they are dissociated in some diseases and associate in others to cause a specific pattern of psychiatric, cognitive and motor symptoms and signs will be essential for highlighting the key functional role(s) of sensory gating and may give novel insights into the neurobiological mechanisms of these symptoms. In particular, as clinician, I am interested to develop some parameters that can be candidate biomarkers for an earlier diagnosis of disease. In this specific case, having a confirmation about the behavior of physiological and perceptual SA in different neurological disorders can lead to the development simple paradigm to test these two parameters in the clinical practice as a biomarker of the disease progression. In the case of physiological SA, recording of SSEPs is already a simple paradigm that might be used in the clinical practice. In this regard, further studies are necessary to test the perceptual SA in PD to compare deficits in perceptual SA to those of physiological SA.

Beta oscillations

During my second project, I then attempted to find a potential correlation of SA with cortical beta oscillations in a cohort of PD patients and age-matched healthy subjects. The reason why I was interested in understanding the functional role of beta oscillations was related to the well-known observation

that PD patients have a pathologically higher power of beta oscillations, both in the cortex (Little & Brown, 2014) and sub-cortically in the subthalamic nucleus (Giannicola et al., 2010; Jenkinson & Brown, 2011; Little & Brown, 2014; Moran et al., 2011). Of note, routine pharmacological treatments for PD as levodopa (Giannicola et al., 2010; Jenkinson & Brown, 2011) and neurosurgical therapies as subthalamic deep brain stimulation (Eusebio et al., 2012; Giannicola et al., 2010; Jenkinson & Brown, 2011; Kuhn et al., 2008) are associated with a decrease in beta power. On the other hand, it is well known that stimulation of the subthalamic nucleus at the beta frequency (15-30 Hz) causes a slowing of movement in patients with PD (Eusebio et al., 2008). Consequentially, Little S and Brown P (Little & Brown, 2014) proposed that the high amplitude of beta oscillations in PD causes bradykinesia. However, the mechanism underlying this hypothesis is still not clear, I hypothesized and then I provided evidence in the studies of chapter 4 and 5 that physiological SA could be the neurophysiological mechanism underlying the bradykinesia. Therefore, if both these mechanisms (physiological SA and high beta power) have been hypothesized as underlying the bradykinesia, I was interested to see if there were any correlations between these two mechanisms. Specifically, I tested whether the modulation of SA was correlated with the modulation of beta oscillations during voluntary movements.

In chapter 5, I tested this hypothesis. I failed to find a significant evidence of modulation of cortical beta oscillations driven by the sensory-motor cortex on SA. This finding can be interpreted in two ways, either that the cortical beta oscillations are not involved in modulation of SA or that our groups' size was not enough to reach the statistical power. Regarding the first

possibility, although there is no direct evidence of a potential link between cortical beta oscillations and SA, it is known that the beta oscillations plays important role on the modulation of motor control. In particular, it has been shown that the modulation of beta oscillations shows a particular pattern during voluntary movements (Pfurtscheller & Lopes da Silva, 1999). Interestingly, this modulation of beta oscillations takes place at the onset of voluntary movement, when SA is also present, suggesting that there is a rationale to explore if the modulation of SA is correlated with modulation in beta power in the sensorimotor cortex. On the other hand, the beta oscillations are present not only at the cortical level but also at the subcortical level as in the basal ganglia, which were not explored in this study. From the above, it is not possible to determine whether or not subcortical beta oscillations play a modulatory role on SA. In order to address this issue further, it would be necessary to investigate SA in PD patients with STN-DBS to test if there is a correlation with the abnormal beta oscillations in STN, typically seen in this group of patients. Regarding the second possibility, it is well known that a major fault of scientific studies (including ours), is inadequate statistical power. A larger number of subjects were required to adequate power the studies, because of increased variability of SA as well as cortical beta oscillations in the patient population. Although this is a major limitation for any conclusion about the mean of potential link between SA and beta oscillations in patients with PD, the fact that SA was replicated to be reduced in patients with PD OFF dopaminergic treatment is noteworthy on its own. Increased variability may have important implications in the design and interpretation of future studies and may indeed be related to pathophysiological mechanisms of PD.

My results did not support the theory suggesting that the modulation of physiological SA and modulation of beta power over the sensorimotor cortex are related. Indeed, I confirmed the modulation of the two parameters during voluntary movements. In particular, I showed in my groups of participants that beta power is reduced just prior to and during the period of movement and is transiently increased subsequent to the end of the movement as it was previously showed by Baker et al.(S. N. Baker et al., 1999; S. N. Baker et al., 1997). Furthermore, Baker et al showed in several studies that beta oscillations play a role in sensorimotor processing (S. N. Baker, 2007; S. N. Baker, Chiu, & Fetz, 2006; Riddle & Baker, 2005; Witham & Baker, 2007) . In this regard, Baker et al. (S. N. Baker et al., 2006) found that beta frequency showed a coherence between proprioceptive afferents (Ia muscle spindles) and forearm muscle activity, suggesting that beta oscillations may have a role mainly in proprioceptive processing. On the contrary, there was no coherence between muscle activity and afferents relate to cutaneous receptors. However, Witham et al. (Witham & Baker, 2007) did not find a difference in coherence with M1 between areas 1 and 3b, which are associated to cutaneous receptive fields, and areas 3a and 2, which are associated with proprioception (areas 3a and 2). Therefore, this study provided evidence for a close link between the sensory and motor systems via oscillatory synchronization and support previous hypotheses that this pattern of activity may be important in coordinating the processing of somatosensory information within its motor context (Riddle & Baker, 2005; Witham & Baker, 2007). In this context, my results did not confirm a role of beta pattern activity in coordinating the somatosensory integration at least in terms of SA. However, I am aware of the limitation that I did not

clean the data from the eye movements and beta oscillations show some changes related with eye movements. This limitation in my analysis is likely to have caused some confounding results.

Furthermore, my study did not show a significant different amplitude in the cortical beta oscillations between PD ON and healthy controls as well as between PD OFF and healthy controls. Therefore, my study brings under discussion the pathological role of sensorimotor beta oscillations in PD. I think that there is a need to repeat the study on a larger group of PD patients to confirm my results. Additionally, further studies are needs to test a potential correlation between physiological SA and beta oscillations generated in the basal ganglia with the aim to test if modulation of SA is correlated with this other pattern of beta activity.

Active Inference

The active inference framework suggests that gating of the afferent signal may be due to a reduction in sensory precision, which is a necessary step in movement initiation (H. Brown et al., 2011). In this regard, my work supports the active inference theory as a good theory regarding motor control. Indeed, two of my studies supported the role of SA as necessary step in movement initiation. Indeed, it was impaired in patients with impaired movement initiation.

At the time we designed the two next projects described in Chapter 6 and 7, previously published studies had provided evidence of a hypothesized link between SA and sensory precision (C. Palmer et al., 2016). Importantly, Tan et al. (Tan et al., 2016) provided a demonstration of a link between a

key parameter in theoretical models of motor control, uncertainty, and modulations in sensorimotor beta power. However, there were no studies testing whether the modulations in beta power are best accounted for by modulations in the uncertainty of the actual sensory input in the contest of the active inference. The second aspect of the active inference framework that I was interested to test was the prediction that modulations in precision were causally correlated with modulations in sensorimotor beta oscillations. This second aspect of active inference was not confirmed by my study described in chapter 5.

These studies tested the prediction from the active inference framework about the uncertainty estimate of the somatosensory signal. My results support this theory. Indeed, I found that the modulation of uncertainty through vibratory stimuli improve the motor performance in healthy subjects as well as PD patients. These results also support the essential role of somatosensory integration in the motor control.

Vibration

In line with the study of Tan et al.(Tan et al., 2016), I reviewed evidence of causal link between a pathology in sensory precision and hypokinetic symptoms of PD. The aim of the studies described in chapter 6 and 7 was to test whether peripheral vibration will reduce sensory precision and therefore reduce bradykinesia. This idea is not new and was first proposed as a treatment for some of the symptoms of Parkinson's disease by Jean-Martin Charcot (Goetz, 2009). Within the active inference framework, the brain has to recognize when sensory information is noisy or uncertain and down weight it suitably in relation to top-down predictions. In other words,

noisy or uncertain sensory input will result in a down weighting of the sensory prediction errors relative to the top-down prediction errors (K. Friston et al., 2011). The rationale behind these two studies was to apply vibrotactile stimulation to the hand to render the sensory signal noisy and uncertain. My hypothesis was that this stimulation would lead to a decrease in sensory precision and therefore a reduction in bradykinesia. In the project described in chapter 6, I showed that peripheral tactile vibration reduced sensory precision and improve the motor performance in healthy participants and PD patients. Thus, I first provided more evidence about the positive impact of a change in sensory precision and motor performance by evaluating the influence of peripheral vibratory stimulus on several motor tasks in healthy controls and PD patients ON medication. Furthermore, in this project, I added the direct electrophysiological evidence of changes in beta power lead by 80 Hz vibration, which may be the underlying mechanism of the improvement in motor performance. I believe that these results described in chapter 6 are interesting because they provide a basis to develop further non-invasive techniques that decreasing sensory precision may improve the bradykinesia. This suggests that peripheral vibration could be a useful method for manipulating motor performance for experimental or clinical purposes. We developed a device generating high frequency of vibration at 200 Hz with two different modulations: 60 bpm and 20 bpm. We found that 200 Hz at 60 bpm lead to a significant improvement of the bradykinesia and precision in drawing tasks in PD patients. This outcome actually provides evidence about another puzzling phenomenon in the motor system, the modulation of sensory proprioception in PD as a tool to improve the clinical features of bradykinesia. These results opened the

wide scenario of developing devices that modulating the sensory signals can improve the motor control and, thus, improving the performance of our voluntary movements. In the study described in chapter 6 I used a device that produced improvement in motor performance with vibration at 80 Hz frequency and with the stimulation for 30 seconds before the performance. In the study described in chapter 7, the tested device produced an improvement of motor performance with a vibration at 200 Hz but only with 60 bpm modulating frequency and with the stimulation during the task. Additionally, the first device could activate the spindle fibers, whereas the second device is likely to work through cutaneous stimulation and, thus, tactile stimulation. I was focused on the upper limbs but it is not likely to be a specific mechanism of motor control for the upper limbs. It is likely that lower limbs are involved in the same mechanisms as several studies focused on whole body vibration or vibration of different part of the bodies showed. These two studies open ideas for further studies because it is important to test the exact mechanisms why vibration with different frequencies improve motor performance and what is the dominant mechanism. Indeed one device suggest a mechanism linked to the spindle fibers and the other on the cutaneous afferents. Studies with micrography are necessary to test the mechanism underlying the improvement of motor performance with vibration.

In conclusion, the studies described above provided significant evidence about the phenomenon of SA and the phenomenon of modulation of sensory precision but they also generated further questions.

Further studies

Here I describe the hypotheses and design of studies that could certainly provide more evidence about these two phenomena, based on the results of this thesis.

1. SA and beta oscillations in BG

In the second study described in Chapter 5 I showed that SA and cortical beta oscillations are modulated differentially at the onset of a brief finger movement. This result raises the question how beta oscillations generated in BG, which are well knows as abnormal in PD, might be correlated to SA. The traditional paradigm for assessment of SA at the onset of movement (which was also used in this thesis) does not allow measurement of subcortical beta oscillations, as the recording is performed through an EEG. However, a different paradigm with recording of leads implanted in the BG as in DBS would allow to test the correlations between the two phenomena. The strength of such correlation will provide direct evidence on the role of SA in defining the kinematic parameters of finger movements. I hypothesize that SA modulation will correlate with the modulation in beta oscillations in BG.

2. Vibratory stimulation and motor performance

A dominant assumption throughout the studies showed in chapters 6 and 8 is that the vibratory stimulation improves the motor performance. Further research is necessary to test different frequencies of vibration to disentangle the question if a specific frequency maximize the positive outcome or if it is a result related to a general vibratory stimulus.

Furthermore, another important aspect to test is the optimum duration of vibratory stimuli to produce the maximum positive outcome. The timing is an important aspect to explore also in relation to the duration of the same positive effect. I think to develop a device with the possibility to change the frequency of vibration and to develop protocol involving vibratory stimulation with different duration.

3. FOG and vibratory stimulation

This exiting result reported in chapter 8 lead myself to test the hypothesis that vibratory stimulation might improve other clinical features of PD as the FOG.

In the next and final study of this thesis I performed a pilot study to test the impact of vibratory insoles shoes on FOG. I based the design and hypothesis of the study on evidence provided by previously published studies. I found a significant improvement of FOG as well as balance in the studied patient. Interestingly, the improvement was more evident during the week after the period wearing the insoles suggesting that vibratory stimulation might have long-term outcome.

A key result of the pilot study described in Chapter 8 was the significant improvement of FOG and, surprisingly, the balance in the studied case. At this point a larger study with 24 PD patients is necessary to give a valid answer to the question if FOG might be improved with vibratory stimuli. Such a study will allow planning for further exploration of different vibratory stimulations as a potential tailored treatment of FOG

In conclusion, this study demonstrated that high frequency vibration applied to the periphery improved motor control on a number of motor tasks in healthy subjects and patients with PD. These results are consistent with a novel theoretical account of motor initiation, namely that modulating uncertainty of the proprioceptive afferent signal improves motor performance potentially by gating the incoming sensory signal and allowing for top-down proprioceptive predictions that incite movement to be more readily fulfilled.

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